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9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

**From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1–3, 1985).

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Vinca Alkaloid-Induced Cardiovascular Autonomic Neuropathy[1]

Enrique Roca, Eduardo Bruera, Pedro M. Politi, Mario Barugel, Liliana Cedaro, Silvia Carraro, and Reinaldo D. Chacón[2,*]

To determine the incidence of vinca alkaloid (VA)-induced cardiovascular autonomic neuropathy (CAN), neoplastic patients were studied. Thirty-three of them were receiving chemotherapy regimens including VAs, and 30 were receiving chemotherapy without VA and were considered controls. Abnormal variation in blood pressure on standing, heart rate during deep breathing, and heart rate on standing was found in 27 (82%), 16 (48%), and 16 (48%) patients receiving VA versus nine (30%; $P < 0.01$), three (10%; $P < 0.05$), and one ($P < 0.001$) controls, respectively. Of 198 tests performed, 100 were abnormal in patients receiving VA (51%) versus 33 of 180 tests in the controls (18%; $P < 0.001$). Although abnormal clinical or electrocardiographic tests for CAN appeared significantly more frequently in patients who received high doses of VA ($P < 0.01$), their incidence was not significantly different in patients ⩾ 60 years of age, in those who received doxorubicin, or in those who showed abnormal deep tendon reflexes. The consequences of VA-induced CAN might be especially important for potentially curable cancer patients. [Cancer Treat Rep 69:149–151, 1985]

Vinca alkaloids (VAs) are widely used antineoplastic agents. Their toxic effects on somatic, bladder, and bowel innervation are well-known (1-3). With the exception of some reports of orthostatic hypotension (4,5), no studies have been previously performed to assess cardiovascular autonomic neuropathy (CAN) induced by these agents. The aim of this prospective study was to determine the incidence and severity of this complication in patients treated with VAs.

PATIENTS AND METHODS

Between April and September 1983, 63 patients with cancer were admitted to the study. Thirty-three of them were being treated with VA-containing regimens and 30 who were receiving chemotherapy without VA were considered controls. The inclusion of VA in the chemotherapy scheme was decided in relation to the histological characteristics. Tumor stages were highly comparable in both groups. No patient had a previous diagnosis of diabetes, arterial hypertension, alcoholism, malnutrition, or mediastinal or cardiovascular disease, and none was being treated with drugs which could modify heart rate or blood pressure. Performance status (Eastern Cooperative Oncology Group-Zubrod) was 2 or less in all patients. Patient characteristics are summarized in table 1.

To assess the cardiovascular autonomic function, clinical and ECG tests were performed. These tests were carried out according to recommendations for the assessment of diabetic autonomic neuropathy (6-8) a mean of 17 days after the last course of chemotherapy.

Clinical tests.—(*a*) Blood pressure changes on standing were measured at the brachial artery with a sphygmomanometer. Failure to increase systolic pressure was scored as pathological response. (*b*) Diastolic pressure modifications during handgrip were tested. Pressure rises of ⩽ 10 mm Hg were counted as abnormal.

ECG tests.—(*a*) Basal heart rate was recorded in D II lead during recumbent position. Values < 60 beats/minute or > 100 beats/minute were considered abnormal. (*b*) Beat-to-beat (R-R interval) heart rate variation was assessed during Valsalva maneuver. The ratio of the longest R-R interval during release to the shortest R-R interval during strain was calculated. Ratios of ⩽ 1.10 were recorded as abnormal. (c) Heart rate changes during deep breathing in the supine position

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[2]Servicio de Oncología, Sanatorio Güemes, Hospital Privado, Buenos Aires, Argentina.

*Reprint requests to: Dr. Reinaldo Chacón, Servicio de Oncología, Sanatorio Güemes, Avenida Córdoba 3933 (1188), F. Acuña Figueroa 1240 (1180), Buenos Aires, Argentina.

TABLE 1.—Patient characteristics*

	VA	Controls	P value†
Total	33	30	
Mean age (yrs)	50.8 ± 10.2	54 ± 11.3	NS
Male/female	8/25	8/22	NS
Primary tumor location			
Breast	21 (64)	20 (66)	NS
Lymphoma	4 (12)	2 (0)	NS
Head and neck	3 (9)	1 (5)	NS
Testicle	2 (6)	0 (0)	NS
Lung	2 (6)	4 (13)	NS
Brain	1 (3)	1 (5)	NS
Colon	0 (0)	4 (13)	NS
Mean cumulative dose (mg)			
Vincristine (n = 31 patients)‡	9 ± 4.6		
Vinblastine (n = 16 patients)	46 ± 24		

* Unless otherwise specified, values = No. of patients (%).
† NS = not significant.
‡ Four patients received both drugs.

(at six breaths per minute) were studied. Rate variation of < 10 beats/minute were considered pathological. (*d*) Continuous ECG recording was performed during standing. R-R intervals at beats 15 and 30 after standing were measured to give the 30/15 ratio. Ratios of ⩽ 1.00 were interpreted as abnormal. Deep tendon reflexes (DTRs) and bowel sounds were evaluated to establish if they could be correlated with CAN. Statistical analysis of data was performed with the Yates-corrected chi-square test for proportions and with the Student's t test for continuous variables.

RESULTS

One hundred of the 198 tests performed in the VA-treated group were abnormal (51%), while 33 of the 180 tests in the control group were altered (18%; $P < 0.001$). Abnormal results for each test are summarized in table 2.

Seventy-six of 156 tests were abnormal in 26 treated patients who were < 60 years of age (49%) versus 24 of 40 in seven treated patients who were ⩾ 60 years of age (57%; P = NS). Eighty-two of 156 tests were abnormal in 26 patients who received doxorubicin-containing regimens (52%) versus 17 of 42 tests in seven patients who did not receive this anthracycline (40%; P = NS). Results according to the cumulative dose of vincristine and vinblastine are summarized in table 3.

Bowel sounds were considered normal in all patients treated with VAs and in all of the control patients.

Seventeen of the 32 patients who received VAs had abnormal DTRs (53%) versus none of 30 controls ($P < 0.001$). One patient who received VAs was not evaluable for DTRs. Incidences of abnormal DTR are summarized in tables 2 and 3. Forty-nine of 102 tests were abnormal in 17 patients who received VA and showed abnormal DTRs (48%) versus 47 of 90 tests in 15 patients who had no abnormal DTRs (52%; P = NS). The incidence of abnormal clinical or ECG tests for CAN was

TABLE 2.—Abnormal results in patients treated with VAs and controls*

	VA (n = 33 patients)	Controls (n = 30 patients)	P value†
Tests for CAN			
Blood pressure on standing	27 (82)	9 (30)	< 0.01
Blood pressure during handgrip	22 (67)	15 (50)	NS
Basal heart rate	7 (21)	2 (7)	NS
Valsalva maneuver	12 (36)	3 (10)	NS
Deep breathing	16 (48)	3 (10)	< 0.05
Heart rate on standing	16 (48)	1 (3)	< 0.001
Total of abnormal tests‡	100/198 (51)	33/180 (18)	
DTRs§	17/54	0	< 0.001

* Data are expressed as No. of abnormal tests (%).
† NS = not significant.
‡ Values = No. of abnormal tests for CAN/total No. of tests (%).
§ Values = No. of abnormal tests for DTR/total No. of tests.

TABLE 3.—Abnormal tests according to cumulative dose of VAs*

	Vincristine ≥ 14 mg or vinblastine ≥ 30 mg (n = 8 patients)	Vincristine < 14 mg or vinblastine < 30 mg (n = 25 patients)	P value†
Tests for CAN			
Blood pressure on standing	7 (88)	18 (72)	NS
Blood pressure during handgrip	7 (88)	14 (56)	NS
Basal heart rate	2 (25)	6 (24)	NS
Valsalva maneuver	4 (50)	7 (28)	NS
Deep breathing	5 (62)	12 (48)	NS
Heart rate on standing	8 (100)	10 (40)	< 0.02
Total of abnormal tests‡	33/48 (67)	67/150 (45)	< 0.01
DTRs§	5/8 (60)	12/24 (50)	NS

* Data are expressed as No. of abnormal tests (%).
† NS = not significant.
‡ Values = No. of abnormal tests for CAN/total No. of tests (%).
§ Values = No. of abnormal tests for DTR/total No. of tests (%).

not significantly different according to the presence or absence of abnormal DTRs.

DISCUSSION

Although orthostatic hypotension was reported in 4% of patients receiving VAs (4), no prospective clinical study has been previously undertaken to assess CAN induced by these agents. Our results show that tests currently employed for the diagnosis of CAN were more frequently abnormal in patients treated with VAs than in a control group. These findings were significantly more frequent in patients who received higher cumulative doses. These data are compatible with the idea of cardiovascular denervation due to VAs.

The tests performed for CAN detection are based on evaluation of both sympathetic and parasympathetic reflex influences on heart rate and blood pressure. These maneuvers have proved to be useful in the assessment of diabetic autonomic neuropathy (6-8). The incidence of abnormal tests was not significantly higher when patients were analyzed according to age (< 60 vs > years), presence (or absence) of doxorubicin in the chemotherapy regimen, characteristics of bowel sounds, or abnormalities in DTRs.

Spontaneous recovery of somatic, bladder, and bowel nervous function (after VA-induced damage) has been described (1,9). Long-term studies are required to establish whether or not CAN is reversible.

Diabetic autonomic neuropathy has been associated with a higher incidence of sudden death and cardiac arrhythmias and respiratory arrest during general anesthesia (10). Further studies are needed to ascertain whether this also proves true for VA-induced CAN. Only one of our patients had clinical orthostatic hypotension, and no cases of sudden death or syncope were found in our CAN group after a mean follow-up of 6 months. The consequences of VA-induced CAN might be especially important for potentially curable cancer patients.

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Long-Term Relapse-Free Survival in Adult Acute Lymphoblastic Leukemia[1,2,3]

Roger D. Gingrich,[4,*] C. Patrick Burns,[4] James O. Armitage,[4] Suzanne B. Aunan,[4] Richard W. Edwards,[4] Fred R. Dick,[5] Lawrence C. Maguire,[4] and J. Thompson Leimert[4,6]

An intensive treatment program with curative intent was designed for adults with acute lymphoblastic leukemia (ALL). Forty-eight consecutive patients were treated with this protocol and 39 (81%) obtained a complete remission. Although the complete remission rate was high for patients with both null- and T-cell disease, those with null-cell leukemia had a significantly greater median duration of remission (> 306 weeks) than patients with T-cell disease (62 weeks). The median survival by life-table analysis for the 48 patients is projected to be > 310 weeks, and five patients have finished the 3-year treatment program and have been off therapy for 1–3 years without recurrence of disease. Classification of adult ALL by immune marker status is an important and easily done pretherapy maneuver that identifies subsets of patients with a significantly different prognosis when treated with the protocol described in this study. Those patients for whom leukemic cells had T-cell characteristics had a short median duration of remission. Most importantly, this treatment protocol identifies by therapeutic response a subset of adult patients with ALL whose leukemic blasts are characterized by the absence of immunological markers and who appear, in substantial proportion, to be potentially curable. [Cancer Treat Rep 69:153–160, 1985]

Although some progress has been made in the treatment of adult acute lymphoblastic leukemia (ALL) in recent years, remission duration and survival have not, in general, approached those obtained in the treatment of childhood ALL. Even though treatment programs used for adults have been similar in regard to drugs and design to those used for children (1), the number of long-term survivors in adult ALL has been disappointingly small. Careful analysis of treatment responses in both childhood and adult ALL has delineated subsets of patients who do much better than others (2–5). Recent studies with monoclonal antibodies to cell membrane antigens have further identified subsets of children with non-T, non-B ALL who have different prognoses (6). However, even with the extensive phenotypic characterization of leukemia cells that is possible with monoclonal antibodies, a satisfactory explanation for apparent differences in the clinical behavior of this disease in children and adults has not been possible (7–9).

The relative contribution to long-term survival that is made by the various phases of treatment has never been clarified in adult ALL. From a hypothetical viewpoint, induction therapy would substantially reduce the initial leukemia cell population and subsequent continuation therapy would either kill the remaining cells or suppress them to the extent that the body's normal defenses could eliminate the remaining neoplastic cells. Indirect evidence from recent studies tends to support the critical importance of continuation therapy in effecting a final cure in adult ALL. It has been repeatedly shown in adult ALL that complete remission rates of 50%–90% can be obtained using vincristine and prednisone combined with an anthracycline (L-asparaginase or cytarabine). When these effective induction programs are followed by con-

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[3]Presented at the American Society for Clinical Oncology meeting, Toronto, Canada, May 9–12, 1984.

[4]Department of Internal Medicine, University of Iowa College of Medicine, Iowa City.

[5]Department of Pathology, University of Iowa College of Medicine, Iowa City.

[6]We acknowledge the assistance of house officers, fellows, and attending staff of our Department of Internal Medicine who participated in the care of our patients.

[*]*Reprint requests to:* Dr. Roger D. Gingrich, Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

ventional forms of continuation therapy like methotrexate and 6-mercaptopurine, a relatively brief median duration of complete remission and poor survival have been seen (10–16). However, when intensive, multiagent continuation chemotherapy is combined with similar induction therapy programs, a substantial increase in the number of long-term survivors can be seen (17–21). This, it seems, indicates that appropriate therapeutic approaches to adult ALL should include more aggressive forms of continuation therapy than have been used conventionally with great success in childhood ALL.

The present study was designed to provide (*a*) an intensive induction regimen composed of four of the most effective drugs known in the treatment of lymphoblastic leukemia (doxorubicin, vincristine, prednisone, and L-asparaginase [HOP-L]), (*b*) effective CNS prophylaxis (22), and (*c*) an intensive, cycling, multiagent continuation regimen modified from the L-10 treatment program designed by investigators at Memorial Sloan-Kettering Cancer Center (23).

METHODS

Patients

Forty-eight consecutive, previously untreated patients seen at the University of Iowa Hospitals were entered in this treatment protocol from July 1977 through August 1983. The median age of the group was 33 years (range, 15–72), with 32 males and 16 females. The diagnosis was based on histochemical staining of the bone marrow aspirate and biopsy. All slides were reviewed by an experienced hematopathologist (F. R. Dick) and reclassified according to the most recent French-American-British (FAB) criteria (24). Surface marker determinations were performed on blasts separated from other bone marrow constituents by density gradient sedimentation. Sheep erythrocyte rosetting was used to demonstrate the T-cell nature of the leukemia (25), and the presence of surface and cytoplasmic immunoglobulin detected by sheep anti-human immunoglobulin antisera was used to delineate the B-cell nature of the disease. Any blast population showing > 5% of the cells marking in either of these two ways was classified as marker-positive. Blasts showing ⩽ 5% of either sheep rbc rosettes or surface immunoglobulin staining were classified as null cells. Terminal transferase assays by immunofluorescence were routinely done on all patients during the latter part of the study (26). Monoclonal antibody reactivity with T101 and anti-CALLA was done on too few patients to be included in this analysis. Cytogenetic data were available on 20 patients and will be presented in a subsequent manuscript.

Treatment

All patients were hospitalized in the Acute Leukemia Unit at the University of Iowa Hospitals for therapy. Remission induction was undertaken with doxorubicin, vincristine, prednisone, and L-asparaginase administered as shown in figure 1. A bone marrow examination on Day 14 was used to determine whether or not more doxorubicin should be given on Days 15–17. If there were < 5% blasts or < 20% cellularity, no further doxorubicin was given. However, if there were > 5% blasts and the marrow cellularity was > 20%, a further course of doxorubicin was given. On Day 31, a second marrow examination was obtained and this was used to determine whether or not the patient went on to CNS prophylaxis (for those in complete remission) or received a third course of doxorubicin (for those not in complete remission). CNS prophylaxis (fig 1) was given over a 2-week period as previously described (22). Continuation therapy was begun immediately with the two treatment sequences as shown in figure 1, administered in an alternating fashion until a total doxorubicin dose of 550 mg/m^2 was reached. After this, patients continued to take sequence II until therapy was terminated at the end of 3 years. Bone marrow aspirates and biopsies were obtained at the end of each sequence to determine the status of the disease. Patients were considered to be in complete remission if they were asymptomatic, had no physical findings suggestive of leukemia, had normal bone marrow aspirate and biopsy, hemoglobin > 10 g/dl, peripheral granulocyte count > 1500/mm^3, and platelet count > 150,000/mm^3.

Supportive Care

During the remission induction phase, patients with a fever > 38.5°C and a granulocyte count < 500/mm^3 were cultured extensively and treated empirically with a cephalosporin and an aminoglycoside antibiotic until the culture results were known. Broad spectrum antibiotics were generally continued throughout the course of neutropenia. Granulocyte transfusions were used only in the setting of a documented severe local or systemic gram-negative sepsis, where the patient showed clinical deterioration, despite appropriate antibiotic treatment. Random donor or HLA-compatible platelet transfusions were given to all patients with evidence of bleeding and were generally given prophylactically when the platelet count was < 10,000/mm^3. Most patients were hospitalized in a single room without special isolation procedures.

Statistical Analysis

The duration of survival was measured from the time of initial therapy and the duration of complete remission was measured from the time of documented remission on bone marrow examination. Duration of survival and continuous complete remission were calculated by the life-table method and statistical evaluations on these distributions were made with the log-rank test (27). All deaths

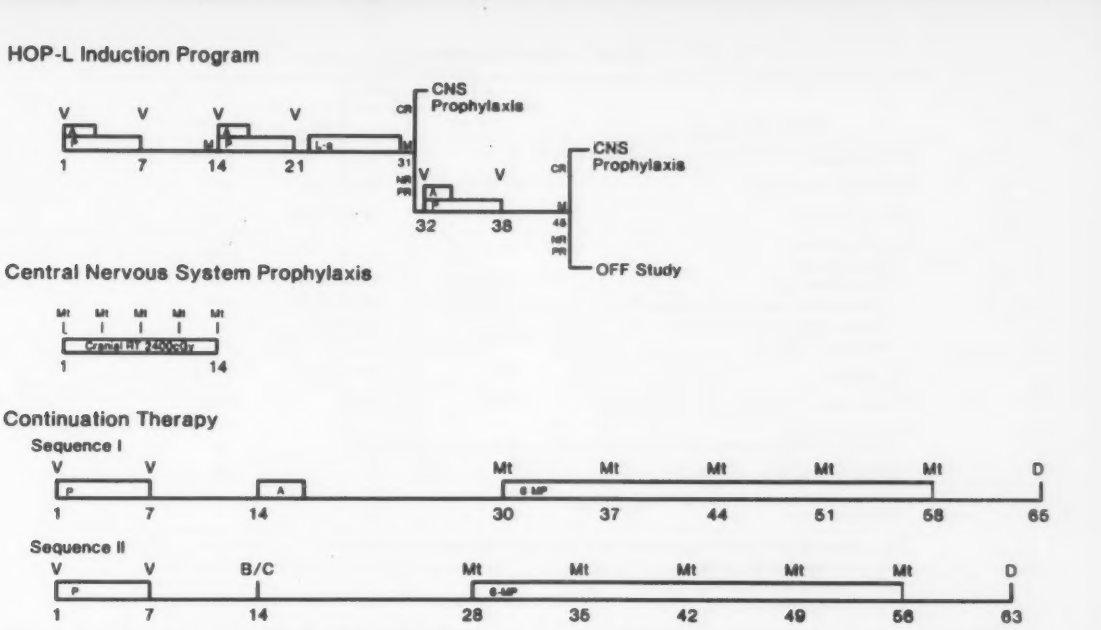

FIGURE 1.—HOP-L induction and CNS prophylaxis. V = vincristine, 1.4 mg/m^2 iv (dose limit, 2.0 mg); A = doxorubicin, 30 mg/m^2/day × 3 days iv; P = prednisone, 60 mg/m^2/day; L-a = L-asparaginase, 10,000 units/m^2/day; Mt = intrathecal methotrexate, 12 mg/m^2 at 1 mg/ml (dose limit, 20 mg); M = bone marrow aspirate and biopsy; CR = complete response; PR = partial response; and NR = no response. Continuation therapy. V = vincristine, 1.4 mg/m^2 iv (dose limit, 2.0 mg); A = doxorubicin, 20 mg/m^2/day × 3 days iv; P = prednisone, 90 mg/m^2/day orally; Mt = methotrexate, 20 mg/m^2 orally; 6-MP = 6-mercaptopurine, 90 mg/m^2 orally; D = dactinomycin, 1000 μg/m^2 iv; B = carmustine, 80 mg/m^2 iv; and C = cyclophosphamide, 800 mg/m^2 iv. Bone marrow aspirate and biopsy are done prior to each dose of dactinomycin. Nos. below the horizontal time line refer to days.

during induction are treated as failures of response, and withdrawals are evaluated up to the time of withdrawal from the study. No patient died disease-free during continuation therapy and none died of causes unrelated to leukemia. No patients were lost to follow-up. Analyses of factors operative in obtaining a complete remission were done by the chi-square method.

RESULTS

Forty-eight consecutive adult patients with ALL were seen at the University of Iowa Hospitals during the treatment period and all were treated with this protocol. All patients, regardless of their clinical condition at presentation or the amount of therapy received during induction, were considered evaluable for analysis. The bone marrow at presentation was hypercellular, with > 50% lymphoblasts in all patients; in most, the lymphoblasts represented > 90% of the cells in the marrow. Table 1 shows a number of features of the total patient population and with regard to their blast cell immune marker status.

Induction of Complete Remission

Overall, 39 of 48 patients (81%) obtained a complete remission. Of 13 patients who were ≥ 50 years of age, eight (62%) obtained a complete remission. The Day 14 bone marrow from 33 patients was < 20% cellular or showed < 5% blasts; therefore, this group received only a single course of doxorubicin during induction. Thirty of these patients obtained a complete remission. The 14 remaining patients with > 20% bone marrow cellularity and > 5% blasts at Day 14 received a second course of doxorubicin. Nine of these patients obtained a complete remission. By chi-square analysis this difference reaches a level of statistical significance ($P = 0.07$). The effect of age (≤ 20 vs > 20 years), initial peripheral blast count (≤ 25,000 vs > 25,000/mm^3), initial serum LDH (≤ 500 vs > 500 IU/L), surface markers, and FAB classification had no significant effect on the rate of induction of complete remission.

Duration of Remission and Survival

Figure 2 shows a life-table plot of the survival of all 48 patients. Fifty-one percent of the entire group is projected to survive at least 310 weeks after diagnosis. The median follow-up on those patients who have remained relapse-free is 104 weeks (range, 12–310). The median duration of complete remission for the entire group is 129 weeks. Figure 3 shows a life-table plot of the prob-

TABLE 1.—Patient characteristics

Characteristic	Immune marker		All patients
	Null cell	T cell	
No. of patients	30	15	48*
Median age in yrs (range)	33 (15-67)	23 (17-72)	33
Sex (male/female)	19/11	11/4	32/16
Initial blood tests			
Median (range)—			
Hemoglobin (g/dl)	10.6 (5.5-17.0)	10.1 (7.8-16.1)	10.8
Lymphoblast count ($\times 10^3$ cells/mm^3)	0.4 (0-543)	26.2 (0-407)	1.9
Platelet count ($\times 10^3$ cells/mm^3)	43 (4-343)	92 (20-257)	52
Serum LDH (IU/L)†	470 (200-4090)	562 (200-6600)	483
TdT positive‡	16/16	3/3	19/19
PAS positive‡	17/28	11/15	28/45
FAB classification§			
L1	11	6	17
L2	17	8	26
L3	0	0	1
Undifferentiated	2	1	3

*1 patient had B-cell leukemia; 2 patients did not have immune marker studies done.
†Normal value, 100-225 IU/L.
‡No. of patients with positive results/No. tested.
§1 patient classified as L1/L2.

ability of remaining in a continuous complete remission as a function of the initial marker status of the leukemic cell population. As can be seen, the median duration of complete remission for patients with T-cell disease is 62 weeks, whereas for patients with null-cell disease 75% are projected to remain relapse-free for at least 306 weeks ($P < 0.001$). Five patients, four with null-cell and one with T-cell disease, have had therapy discontinued and remain free of disease for 52+ to 172+ weeks since their last treatment. There have been a total of 15 disease relapses. Eight relapses were initially in the bone marrow, three in the testes, three in the CNS, and one patient relapsed simultaneously in the bone marrow and CNS. Three of the relapses occurred in patients with null-cell disease, 11 occurred in patients with T-cell disease, and the remaining occurred in a patient in whom immune marker data were not available. Two patients in first complete response withdrew for allogeneic bone marrow transplantation.

Individual features, in addition to immunological

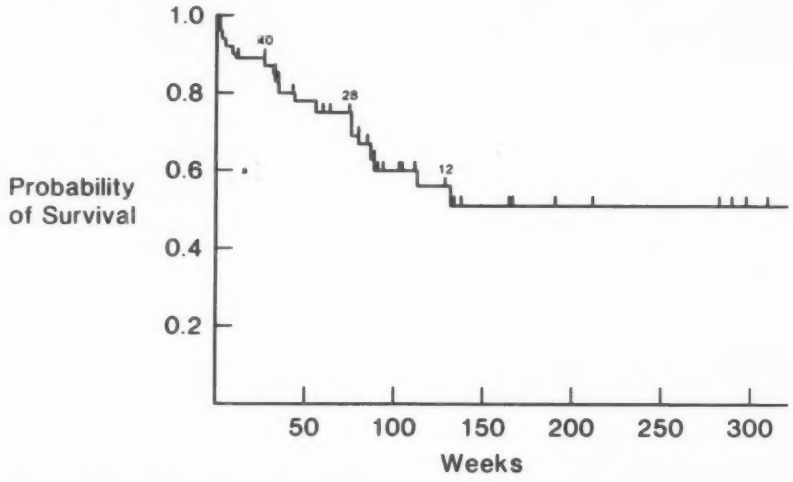

FIGURE 2.—Life-table analysis of survival for all patients. Nos. above the graphed line refer to the No. of patients at risk.

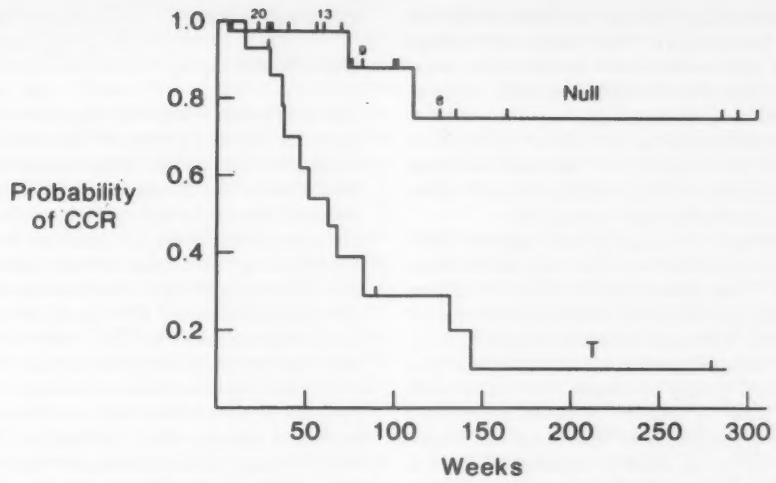

FIGURE 3.—Life-table analysis of continuous complete remission (CCR). Null = plot of CCR for 23 patients with null-cell leukemia; T = plot of CCR for 14 patients with T-cell leukemia. Nos. above the graphed lines refer to the No. of patients at risk.

markers, that may have influenced the duration of remission were analyzed with the log-rank test. Table 2 shows that of the factors analyzed, only the initial peripheral blast count and surface marker classification correlated significantly with the duration of complete remission.

Toxicity

Although most patients experienced some degree of toxicity during the induction phase of this program, this was judged to be acceptable and did not warrant any protocol changes. The mean hospital stay during induction was 52 days and, thereafter, all treatment was given on an outpatient basis. A mild-to-moderate amount of gastrointestinal toxicity, which included nausea and vomiting, was seen almost uniformly during the induction phase. This, in most instances, was well-controlled with antiemetic therapy.

Although fevers of > 38.5°C were almost uniformly observed during the period of neutropenia, only nine pa-

TABLE 2.—Univariate analysis of characteristics associated with continuing complete remission

Characteristic	No. of patients	Median duration of complete response (wks)	*P* value
Age (yrs)			
⩽ 20	12	72	0.28
> 20	27	129	
Initial blast count ($\times 10^3$ cells/mm^3)			
⩽ 25,000	30	139	0.011
> 25,000	9	49	
Initial serum LDH (IU/L)			
⩽ 500	17	80	0.13
> 500	22	61	
Immune markers			
T cell	14	57	< 0.001
Null cell	23	> 306	
FAB classification			
L1	15	60	0.29
L2	21	82	
Received doxorubicin on Day 15			
Yes	9	74	0.1
No	30	61	

tients had a documented bacterial infection (seven were gram-negative bacteremia) and one patient had a fungal infection, for a documented septic complication rate of 21%. Three patients (6%) died of uncontrolled sepsis acquired during the neutropenic period.

Profound thrombocytopenia was also a very common finding, although in no instance did this result in a major hemorrhagic complication. Eight patients did not require platelet transfusions during their hospital stay.

The administration of L-asparaginase was associated with biochemical abnormalities in over one-half of the patients; however, these abnormalities prompted a clinical decision to reduce the amount of L-asparaginase given in only four patients. This dose reduction was due to an increase in serum amylase associated with abdominal pain in one patient and rapidly increasing liver function abnormalities in three. A total of 24 patients developed liver function test abnormalities, with the most frequent being an elevation in the alkaline phosphatase (median elevation was 3.2 times normal). Twenty-five of 35 patients from whom laboratory data were obtained developed coagulation abnormalities, but in none did this necessitate the discontinuance of L-asparaginase therapy and in none were the coagulation abnormalities associated with clinical hemorrhage.

Ten patients showed a moderate degree of myelosuppression during L-asparaginase treatment as defined by either a platelet count of $< 100{,}000/mm^3$ or a wbc count of $< 1500/mm^3$. In none were these values of clinical significance. Thirty-five of the 39 patients who obtained a complete remission received full-dose intrathecal methotrexate and cranial irradiation for CNS prophylaxis. Four patients had the intrathecal methotrexate reduced by one or two doses because of myelosuppression (three patients) or arachnoiditis. No other immediate or long-term sequelae from cranial irradiation were seen.

Continuation therapy was generally very well-tolerated and most patients were able to return to their predisease performance status. Four patients required brief hospitalizations during neutropenic periods for fevers without a documented sepsis. One additional patient did have nonfatal documented *Escherichia çoli* bacteremia; otherwise, no life-threatening toxicity was encountered.

With the significant difference in the duration of complete remission, it was of interest to determine the amount of continuation therapy that patients with either T-cell or null-cell disease received. Hence, the proportion of treatment sequences in which there was no, or only minimal, dose reduction (< 25% or a delay in the administration of drug by ≤ 7 days) was calculated. For the T-cell patients, a mean of 75% of their treatment sequences was given at no or minimal reduction; however, for the patients with null-cell disease, the mean percentage of sequences given without significant dose reduction was 42%. Delays in the administration of drug or the dose reduction were almost uniformly the result of myelosuppression.

DISCUSSION

It has become abundantly clear over the past several years that the adult form of ALL is different from the childhood form, despite their morphologic similarities. Several important therapeutic variables have been identified that account for the excellent results obtained in the treatment of childhood ALL. They are the combination of vincristine and prednisone with at least one other effective antileukemic drug in the induction phase of therapy, the administration of CNS prophylactic therapy, and continuation therapy for 2-3 years of complete remission. The preservation of the complete remission status in children appears to rest on all three phases of therapy and most importantly includes an effective postinduction treatment regimen (1). Continuation therapy with a combination of methotrexate and 6-mercaptopurine has been shown to be as effective as any regimen, including those that have combined those two drugs with a third or even a fourth drug (28,29). Despite the effectiveness of these programs, approximately one-half of children with ALL relapse and die of drug-resistant disease. A recent assessment of these results in childhood ALL led to the suggestion that the appearance of drug-resistant disease during continuation therapy might be avoided by using a cycling, multidrug, non-cross-reactive regimen (1). Implications of recent theoretical work on the kinetics of the appearance of drug resistance in tumors support the validity of this approach (30,31).

Treatment programs in adults with ALL have adopted some of the treatment approaches suggested from the study of childhood disease. While comparable rates of induction of complete remission have been reported, few treatment programs have been able to extend the median duration of complete remission beyond 1 year (10-16, 32). An increased number of adult ALL patients surviving without disease beyond 1 year has been seen in studies employing an induction phase of therapy that is clearly more intensive than that usually given in childhood disease (18,33,34) or a more intensive continuation therapy program (18,21,35). The results of the L-10 and L-10M treatment programs from Memorial Sloan-Kettering Cancer Center have produced a clear indication that intensive therapy, in both the induction/consolidation phase and the continuation phase of treatment, is necessary if the treatment results seen in childhood disease are ever to be approached in adults with this disease (18,34). Two additional studies reporting excellent results in adult ALL have focused on subsets of patients with good prognostic features. Both reports contained patients with a very young median age and one studied only patients with null-cell ALL (19,20).

Thus, there is a suggestion that adults with ALL can obtain long-term, disease-free survival if appropriate

treatment regimens are given. The treatment regimen in the present study was designed with curative intent by using some approaches that had been successful in treating childhood ALL. Hence, four of the most effective drugs in ALL were administered during the induction phase of the program. For patients obtaining a complete remission, a combination of CNS irradiation and intrathecal methotrexate was given as CNS prophylaxis. A distinct phase of consolidation therapy was not given. A modification of the Memorial Sloan-Kettering L-10 continuation therapy program (18) was then administered to those patients in complete remission for a period of 3 years after which all therapy was discontinued. Our results indicate that the HOP-L induction program is highly effective in inducing complete remission in adults with ALL. In addition, the median duration of complete remission for all patients of > 2 years is among the best reported. Most importantly, however, is the identification of the subset of adult patients with null-cell disease, a high proportion of whom are enjoying long-term, disease-free survival and may have been cured by this treatment program.

The excellent results reported recently by Schauer et al (18) at Memorial Sloan-Kettering Cancer Center prompts a comparison of our results. The two treatment programs differ significantly, with both the L-10 and L-10M regimens being much more intensive than our regimen, especially in the consolidation phase where there is intensive exposure over 3 months to cytarabine, 6-thioguanine, systemic methotrexate, cyclophosphamide, L-asparaginase with or without vincristine, prednisone, and irradiation to bulky disease. No comparable treatment was given to our patients. We have used cranial irradiation and intrathecal methotrexate as CNS prophylaxis and have seen four of 15 relapses in the CNS. The L-10 program has relied on intrathecal methotrexate extended throughout the 3 years of continuation therapy and has documented five of 21 relapses in the CNS. Since CNS prophylaxis from neither treatment program resulted in significant early or late sequelae and CNS relapse rates are similar, the approach that is simpler would seem better. We would continue to favor the 2-week course of cranial irradiation plus intrathecal methotrexate. Continuation therapy for the two programs is similar except that our regimen is modified to include no intrathecal methotrexate and a lower dose of vincristine. The septic complication rate from the Memorial programs was two to three times that documented in our experience, attesting to the greater intensity of the former. While the duration of complete response for the entire group is slightly better for the L-10/L-10M-treated patients, fewer patients with T-cell disease attained a complete response and, therefore, were at risk for relapse. Although there were only 13 patients with T-cell ALL in the Memorial Sloan-Kettering study, patients with T-cell disease did not appear to have a poorer prognosis, in contrast to results presented in this paper. The uncertain prognostic value of the T-cell subtype in childhood (36) and adult (37) forms of ALL has also been noted by others. Three observations may be offered. We have defined T-cell ALL as disease with > 5% T lymphoblasts. The criteria for distinguishing between T-cell and null-cell disease are poorly defined in the literature, and some centers would demand a higher percentage. We reasoned that it might be biologically, as well as statistically, meaningful if > 5% of leukemic cells had the T-cell phenotype. Thus, we arrived at our criteria. Second, some prognostic factors may operate independently of the type of therapy given (eg, the peripheral lymphoblast number was a significant variable in both studies), while others may or may not have significance depending, apparently, on the therapy [eg, immune markers or proliferative activity of the leukemic blasts (38)]. This assumes, of course, that the patient populations are comparable. A third observation is that L-10/L-10M therapy is perhaps more intense than required, particularly regarding the consolidation phase, for most adults with ALL, ie, those with non-B-, non-T-cell disease. By contrast, our regimen has been insufficient for those patients with T-cell lymphoblastic leukemia.

In summary, we have presented the results from an intensive treatment program for adults with ALL who show an 81% complete remission rate and a median duration of complete remission of 126 weeks. These results represent a dramatic improvement on the results we have previously obtained for the treatment of adult ALL (11) and are among the best in the current literature. Moreover, this study has identified a subset of adults with ALL (null-cell disease) who appear to be cured by our treatment program, making more intensive (and more toxic) therapy unnecessary and abrogating the necessity for considering early bone marrow transplantation (39-41). Clearly, patients with T-cell disease have not achieved long-term, disease-free survival in substantial numbers with this current program and these patients should be approached with more intensive therapy.

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Intensive Alternating Chemotherapy Regimen in Small Cell Carcinoma of the Lung[1,2]

Maurie Markman,[3,4] Martin D. Abeloff,[3,*] Aron W. Berkman,[3] and William C. Waterfield[3,5]

Fifty-five patients with small cell carcinoma of the lung (SCCL) were treated with alternating courses of CAV (cyclophosphamide, doxorubicin, and vincristine) and VHM (etoposide, hexamethylmelamine, and methotrexate) at 21-day intervals. One regimen contained high-dose cyclophosphamide (2400 mg/m² iv), while the second contained an increased dose of etoposide (250 mg/m² iv on Days 1–3). Patients achieving a complete response (CR) received a minimum of six cycles of therapy or two cycles beyond the achievement of CR. These patients as well as those with partial response with disease limited to the lung then received radiotherapy to the lung primary (5100 rads in 300-rad fractions) as well as prophylactic cranial radiotherapy (3000 rads in 300-rad fractions). All therapy was subsequently stopped until relapse. There were no deaths during the aplastic periods induced by the intensive chemotherapy. CR was achieved in 57% of the patients and partial response was achieved in 38%. The actuarial median survival for the 27 patients with extensive disease was 13.5 months and for the 28 patients with limited disease was 13 months. Survival at this point appears comparable to less intensive regimens in which maintenance therapy was given. We conclude that prolonged intensive induction chemotherapy in SCCL is well-tolerated. Studies are needed to examine in a randomized trial the role of alternating combinations and maintenance therapy in SCCL. [Cancer Treat Rep 69:161–166, 1985]

In recent years several groups of investigators have attempted to increase the complete response (CR) rate and survival in small cell carcinoma of the lung (SCCL) by the intensification of treatment regimens (1–9). The ability to safely deliver intensive therapy under carefully controlled conditions to this patient population has clearly been demonstrated (10). Unfortunately, there is at present no definite evidence that such treatment programs are superior to lower dose outpatient combination chemotherapy regimens (1).

One possible explanation for this is that most intensive chemotherapeutic protocols have called for the administration of only one or two induction cycles of intensive therapy, with subsequent treatment being with the same or alternate drugs at considerably lower dosages. Additionally, in the regimens reported to date, intensive therapy has essentially meant "intensive alkylating therapy," with cyclophosphamide usually being the agent escalated in dose.

Since 1977, a series of intensive combination chemotherapy protocols for SCCL have been investigated at The Johns Hopkins Oncology Center (6–9). We recently instituted a study to test whether prolonged intensive induction therapy using alternating combination chemotherapeutic regimens without maintenance therapy could significantly increase the CR rate and survival in SCCL as has been suggested in a mathematical model of tumor growth and drug resistance developed by Goldie and Coldman (11). The alternating regimens of CAV (cyclophosphamide, doxorubicin, and vincristine) and VHM (etoposide, hexamethylmelamine, and methotrexate) have each been shown to be effective in SCCL (12,13). In addition to high-dose cyclophosphamide administered in the CAV regimen, the dosage of a second highly active

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[3]The Johns Hopkins Oncology Center, The Johns Hopkins University School of Medicine, Baltimore, MD.

[4]*Present address*: Division of Hematology/Oncology, Department of Medicine, University of California, San Diego.

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[*]*Reprint requests to:* Dr. Martin D. Abeloff, The Johns Hopkins Oncology Center, First Floor, Rm 128, 600 N Wolfe St, Baltimore, MD 21205.

agent, etoposide, was increased in the VHM regimen. Finally, following the completion of the chemotherapy program, patients achieving CR or partial response (PR) with residual disease limited to the chest received chest and prophylactic cranial radiotherapy (PCR) in an attempt to decrease the incidence of local recurrence and CNS metastasis. This report describes the result of this treatment approach in 55 patients with limited and extensive SCCL who have a minimum of 1 year follow-up from the initiation of therapy.

TABLE 1.—Chemotherapy treatment protocol*

Drug	Dose	Route	Day
CAV—Cycles 1, 3, and 5			
Cyclophosphamide	2400 mg/m^2	Iv	1
Doxorubicin	70 mg/m^2	Iv	1
Vincristine	1.4 mg/m^2	Iv	1
VHM—Cycles 2, 4, and 6			
Etoposide	250 mg/m^2	Iv	1-3
Hexamethylmelamine	10 mg/kg	Oral	1-5
Methotrexate	30 mg/m^2	Iv	1

* Cycles are alternated at 21-day intervals.

PATIENTS AND METHODS

Fifty-five previously untreated patients with SCCL (36 male and 19 female; median age, 58 years) were treated with the chemotherapeutic regimen described below. Patients excluded from this protocol included those > 70 years of age, those with evidence of brain metastasis at presentation, and those with Eastern Cooperative Oncology Group (ECOG) performance (PS) status of 4 (unless the medical problems were secondary to the tumor). Pretherapy evaluation included routine hemogram, serum electrolytes, liver and renal function tests, liver scan, bone scan with x-rays of areas positive on scan, bronchoscopy, marrow aspirates and biopsies from bilateral posterior iliac crests, and computerized tomographic (CT) scans of the chest and mediastinum. A CT scan of the brain was only obtained if the patient had symptoms suggestive of CNS involvement with tumor. Limited disease (LD) was defined as disease limited to one hemithorax, including disease involving ipsilateral supraclavicular nodes or pleural effusions. Extensive disease (ED) was defined as disease not limited to one hemithorax. Twenty-eight patients had LD, while 27 patients had evidence of ED. Eight patients (15%) had liver metastasis, 20 (36%) had bone metastasis, 13 (24%) had documented bone marrow involvement with tumor, 16 (29%) had pleural effusions, and 12 (22%) had supraclavicular node involvement. Twelve patients (22%) had evidence of a postobstructive pneumonia at presentation, while seven (13%) demonstrated clinical evidence of a superior vena caval syndrome. Thirty-three patients (60%) had an ECOG PS of 0 or 1 at the time of initiation of therapy, 11 (20%) had a PS of 2, and 11 (20%) had a PS of 3 or 4.

The basic treatment plan was the administration of six cycles of two alternating intensive combination chemotherapy regimens (CAV, VHM) at 21-day intervals (table 1). If the wbc count had not reached 3500/mm^3 on Day 21, therapy was delayed 1 week. The first 28 patients were treated in the manner described in table 1. The final 27 patients received the same therapy with VHM being administered during Cycles 1, 3, and 5 and CAV being administered during Cycles 2, 4, and 6. By administering the VHM combination first, we hoped to evaluate the activity of this regimen prior to the addition of CAV. In addition, it was felt that should the VHM combination be found to be comparable to CAV in induction and rapidity of response, it could possibly substitute for this regimen in those situations where it was desired to avoid the use of doxorubicin (cardiac dysfunction, concomitant radiotherapy and chemotherapy). There was no significant difference between the groups initially treated with CAV or VHM in percentage with ED versus LD or with PS 0 or 1 at presentation.

Patients achieving a CR prior to Cycle 5 completed six cycles of chemotherapy and then received radiotherapy to the lung primary as well as PCR (described below). All treatment was subsequently stopped until relapse. Patients achieving a CR after Cycle 5 were treated for two cycles beyond the attainment of CR (if it was believed they could tolerate the therapy). Chest radiotherapy and PCR were subsequently delivered and therapy was then stopped. Patients failing to achieve a CR but having residual disease limited to the chest in technically feasible radiotherapy ports received the radiotherapy described below. All other patients who failed to achieve a CR or who progressed while on therapy received no additional treatment as part of this protocol and were eligible to participate in phase I and II studies of new agents in SCCL.

All patients achieving a CR and those with PR as described above received chest radiotherapy beginning approximately 5 weeks after their last course of chemotherapy. In most patients, the primary tumor, mediastinum, and ipsilateral supraclavicular lymph nodes received 3000 rads in ten fractions and, following a 2-week break, an additional 2100 rads in seven fractions. The spinal cord was blocked at 3000 rads. Treatment simulation was performed routinely in all patients receiving radiotherapy, a shrinking-field technique was employed, and treatment was given to the postinduction chemotherapy treatment volume. PCR was administered at the same time as the initial chest radiotherapy (3000 rads in ten fractions). Patients presenting with postobstructive pneumonia were initially treated with a single fraction of 600–1000 rads to the obstructed bronchus 3 days prior to the institution of chemotherapy. Patients with evidence of obstruction but without pneumonia (no fever) or with

the superior vena caval syndrome were treated with chemotherapy alone.

Patients were admitted to the hospital for hydration prior to the administration of high-dose cyclophosphamide (CAV cycles). Patients then able to go home were discharged to be readmitted on Day 7 or 8 to remain until bone marrow recovery. VHM was administered on an outpatient basis, with the etoposide being given as a 3-hour infusion to avoid hypotension. Patients receiving this regimen were initially all readmitted to the hospital on Day 8, but when it became apparent that the degree of leukopenia was milder than expected, patients were, for the most part, able to be managed completely as outpatients during the VHM cycles. Our approach to the management of the hematologic and infectious problems seen during the severe bone marrow aplasia induced by this therapy has previously been described (10).

Definition of Response

CR was defined as normalization of all initially abnormal radionuclide scans, x-rays, and laboratory tests. If initially positive, the bone marrow had to show no evidence of tumor. Additionally, a CT scan of the chest had to reveal no evidence of residual tumor and if the patient had abnormal bronchoscopic findings at presentation these had to normalize.

PR was defined as a reduction of at least 50% of the products of the longest perpendicular diameters of the measurable lesions lasting at least 1 month, with no evidence of new lesions during this period of time. Patients with evaluable but nonmeasurable lesions had to demonstrate definite improvement in evaluable malignant disease estimated to be > 50% and agreed upon independently by two investigators. A PR of a malignant effusion needed to be clearly related to antineoplastic therapy. A PR of bone metastases was defined as a 50% decrease in the size of lytic lesions on x-ray, with no evidence of progression elsewhere in bone lasting for at least 4 weeks. A bone scan abnormality had to completely disappear to be considered evidence of response to treatment.

No response was defined as a < 50% decrease in the sum of the products of the perpendicular diameters of the measurable lesions.

Progressive disease was defined as an increase in any measurable lesion by > 25% in the sum of the products of the perpendicular diameters of the measurable lesions, the appearance of any new areas of disease, or the deterioration due to tumor in PS by two score levels.

Statistical Analysis

Duration of response and survival were calculated from the first day of chemotherapy and were analyzed by the actuarial method of Kaplan and Meier (14). Comparison of these curves was performed using the log-rank test (15).

RESULTS

Of the 55 patients entered in the protocol, 53 are eligible for evaluation of response to therapy (table 2). All patients are included in the analysis of survival. Two patients withdrew from the study because of prolonged aplasia during the initial CAV cycle. Of the 53 evaluable patients, 50 (94%) achieved at least a PR, including 24 of 26 patients (92%) with LD and 26 of 27 patients (96%) with ED. Sixty-two percent of patients with LD (16 of 26) and 52% of patients with ED (14 of 27) achieved a CR, and two patients (8%) with LD and one patient (4%) with ED failed to achieve at least a PR.

The actuarial curve for relapse-free survival of the complete responders is shown in figure 1. Median time to relapse was 12.5 months, with five of the 30 complete responders still in remission. There were no statistically significant differences in the relapse-free survival times of complete responders who presented with LD or ED.

The actuarial median survival for the 28 patients with LD was 13 months, while the corresponding value for the 27 patients with ED was 13.5 months. The overall actuarial survival for the 55 patients is shown in figure 2. The median survival for the complete responders (18 months) was significantly longer than that for the partial responders or nonresponders (11 months) (fig 2).

Patients receiving either CAV or VHM as initial therapy appeared to have similar rates of disease regression in the lung. In addition, there was no apparent difference between the two initial treatment regimens in the rate of disease regression in the liver, bone, or marrow, although these latter sites of disease involvement are much more difficult to evaluate. Finally, there was no difference in the CR rate between patients treated initially with CAV or VHM (54% vs 59%) or in the time to relapse in patients achieving CR.

At this point, 42 of the 50 responding patients have relapsed (84%), including 19 of 24 patients with LD and 23 of 26 patients with ED. Three patients with LD (13%) and two with ED (8%) remain in unmaintained CR, with a median follow-up of 22 months. Three of the 30 patients (10%) achieving CR who received radiation therapy to the chest have recurred solely at the primary site, six complete responders (20%) recurred at the primary site as well as at other locations, and 16 complete responders relapsed at extrathoracic sites only. Three of these complete responders were unable to complete the planned course of chest irradiation. Four patients (13%) achieving CR who received PCR developed brain metastasis from 4 to 16 months following the completion of therapy. In three of these patients, the brain was the only site of relapse.

Further analysis of the 16 patients with LD who

TABLE 2.—Response to CAV/VHM chemotherapy regimen (53 evaluable patients)

Response	No. of patients (%)		
	Total (n = 53)	LD (n = 26)	ED (n = 27)
CR + PR	50 (94)	24 (92)	26 (96)
CR	30 (57)	16 (62)	14 (52)
No response	3 (6)	2 (8)	1 (4)

achieved a CR shows that three patients remain in CR, two relapsed at the primary site alone, two relapsed at the primary site and liver, and eight relapsed at the extrathoracic sites (either liver or brain). One patient with LD who achieved a CR died due to neurologic deterioration of unknown etiology.

Detailed analysis of toxicity is evaluable for the first 44 patients treated in this protocol. As anticipated, the major toxic effects of therapy were related to the significant bone marrow aplasia induced by the chemotherapy regimens. The mean duration of wbc count depression < 1000/mm^3 during the CAV cycles was 6 days. One hundred and twenty-nine courses of CAV were administered. Fever occurred during 48% of cycles. Severe thrombocytopenia (platelet count < 30,000/mm^3) developed during 36% of courses, increasing from 19% in Cycles 1 and 2 to 58% in Cycles 5 and 6. A single episode of significant gastrointestinal bleeding occurred in the 129 courses of CAV. Documentation of hematologic toxicity during the VHM cycles was less complete, since patients were, for the most part, treated completely on an outpatient basis. One hundred and twenty-three courses of VHM were delivered and only during 21 courses (17%) was any temperature elevation noted. Severe thrombocytopenia, while occurring only during 17% of Cycles 1 and 2, developed in 43% of Cycles 5 and 6. There were no significant bleeding episodes subsequent to the VHM cycles.

Two patients discontinued intensive therapy after the first cycle (CAV) because of prolonged bone marrow aplasia. The patient who developed the severe thrombocytopenia and gastrointestinal bleeding had his subsequent treatment given at a somewhat lower dose without recurrence of bleeding. Two patients were not able to complete their course of chemotherapy because of prolonged severe thrombocytopenia following Cycle 5 (CAV). All of the other patients eligible to receive six cycles of intensive chemotherapy were able to do so. Eight patients have received full-dose treatment beyond six cycles without significant difficulty. There were no deaths during the episodes of aplasia induced by the chemotherapeutic regimens.

DISCUSSION

Clinically meaningful and often dramatic responses to chemotherapy can be rapidly achieved in most patients

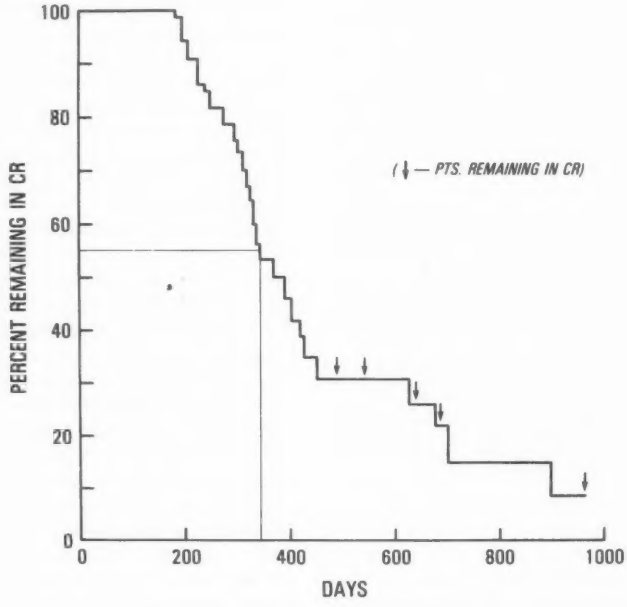

FIGURE 1.—Time to relapse of patients in CR (n = 30).

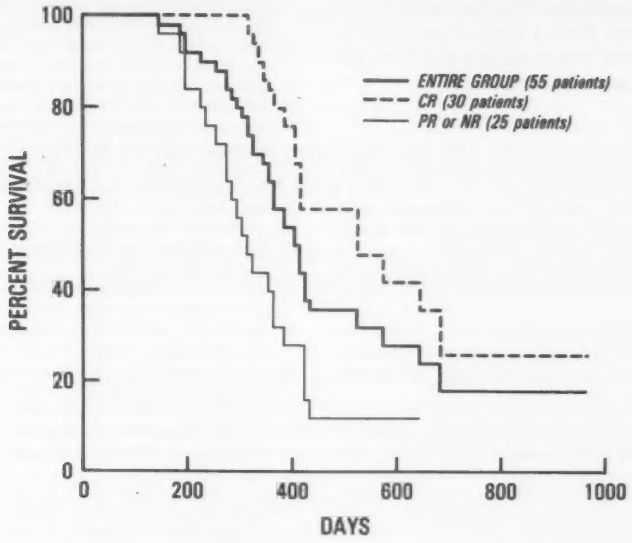

FIGURE 2.—Survival from initiation of therapy for the entire patient population (55 patients), those achieving CR (30 patients), and those failing to achieve CR (25 patients).

with SCCL. Despite these gratifying tumor regressions, durable CRs do not occur in most patients, and long-term survival, even with apparently localized disease, remains uncommon (1).

Recent approaches to the problem of residual and recurrent SCCL have included the use of alternating chemotherapeutic regimens, intensification of therapy, use of new agents, and combined use of chemotherapy and radiotherapy (1–9,16). In the study reported we have incorporated three of these approaches utilizing alternating courses of two intensive chemotherapeutic regimens in an effort to decrease the probability of the emergence of a multiply resistant clone of tumor cells [based on the mathematical model of tumor cell kill developed by Goldie and Coldman (11) and supported by recently completed trials in Hodgkin's disease (17) and diffuse histiocytic lymphoma (18)]. Patients achieving a CR or PR with disease limited to the chest subsequently received maximal radiotherapy to the lung primary as well as PCR. In theory, it would be desirable for the chemotherapeutic regimens to be non-cross-resistant as well as equally (and highly) effective against SCCL. Although these ideals have not been accomplished, both CAV and VH (without M) regimens have, in fact, been shown to be active in SCCL (12,13).

Several points can be made in evaluating the results of our study. On the positive side, the overall response rate was 94%, with CR rates of 62% in patients with LD and 52% in patients with ED.

We have demonstrated the ability to deliver prolonged intensive induction therapy without increasing treatment-related deaths. Of perhaps more interest, we have begun to escalate the dose of a nonalkylating agent, etoposide, in combination with other agents active in SCCL. While we did not directly compare the VHM to CAV combinations in a randomized trial, no significant difference was observed in the response rate to the two combinations and survival was not different in the two treatment regimens.

Unfortunately, relapses continue to occur during and following the completion of therapy. To date, 83% of patients who achieved CR, which included normalization of CT scans of the chest and bronchoscopic findings, have relapsed. Although definitive radiotherapy was delivered to all patients achieving CR following the completion of chemotherapy, relapse at the site of the primary lesion was frequently observed. Overall survival for both patients with LD and ED is similar to our previous intensive combination chemotherapeutic regimens and to that reported in the literature (median survival, 10–14 months) (1,8,9).

Finally, we have demonstrated that induction therapy consisting of intensive chemotherapy courses of two alternating combination regimens followed by definitive radiotherapy appears to give results similar to other reported regimens which continue treatment for 1–2 years. Whether continued therapy would have been beneficial to a subgroup of patients achieving CR cannot be determined in this study. The role of alternating induction regimens and the role of maintenance therapy in patients

achieving CR in SCCL is worthy of further study in prospective randomized trials. Such a study is currently being performed in patients with extensive SCCL by the ECOG on the basis of this study.

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Effect of Adjuvant Central Iv Hyperalimentation on the Survival and Response to Treatment of Patients With Small Cell Lung Cancer: A Randomized Trial[1,2]

Gerald H. Clamon,[3,*] Ronald Feld,[4] William K. Evans,[4] Roy S. Weiner,[5] Edgar M. Moran,[6] Ronald H. Blum,[7] Barnett S. Kramer,[5] Robert W. Makuch,[8] Freddie A. Hoffman,[8] and William D. DeWys[9,10]

The effect of central iv hyperalimentation (IVH) as an adjunct to aggressive antineoplastic therapy for small cell carcinoma of the lung was evaluated in a randomized trial with 119 evaluable patients. IVH was given over a 28-day period with higher caloric and protein intake for patients nutritionally depleted on entry in the study; all patients were escalated in caloric and protein intake to maximize nutritional repletion. Combination chemotherapy and radiation therapy induced a 45.5% complete response rate and an overall response rate of 92.8%. Median survival for patients with limited disease was 18 months; median survival for patients with extensive disease was 11 months. Patients randomized to receive IVH did not have a better response rate ($P = 0.97$) or survival ($P = 0.78$) than control patients. IVH did not significantly alter the survival for patients who at baseline had > 5% pretreatment weight loss, low caloric intake, decreased serum albumin, or reduced total iron-binding capacity. Significantly more febrile episodes were seen in IVH patients than in control patients ($P < 0.001$). Short-term IVH to patients with this malignancy who are capable of enteral alimentation cannot be routinely recommended as adjunctive therapy. [Cancer Treat Rep 69:167–177, 1985]

Weight loss has been shown to be an indicator of poor prognosis in cancer patients (1) and in lung cancer patients in particular (2). Early studies of central iv hyperalimentation (IVH) suggested that reversal of weight loss and malnutrition at the beginning of antineoplastic therapy would increase response to therapy, improve survival, and ameliorate toxicity (3–5). Subsequent randomized trials failed to substantiate such benefit when applied to patients, regardless of their initial nutritional deficit (6–8). Reviews have suggested that only the markedly malnourished should receive IVH (9) and that adequate IVH must be given to replenish the patient (10). A study of patients with colorectal carcinoma and hepatic metastases demonstrated decreased survival in those receiving IVH (11). The benefits of IVH might be anticipated to be more apparent when applied to small cell cancer of the lung (SCCL), a disease in which weight loss is common and prognostically significant and for which more effective chemotherapy exists (12,13).

In 1979, we initiated a phase II trial in which 128 pa-

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[3]Department of Medicine, University of Iowa College of Medicine, Iowa City.

[4]Department of Medicine, University of Toronto, Ontario, Canada.

[5]Department of Medicine, University of Florida, Gainesville.

[6]Department of Medicine, University of California, Irvine.

[7]Department of Medicine, New York University, New York, NY.

[8]Biostatistics and Data Management Section (*R. W. Makuch*) and Clinical Investigations Branch (*F. A. Hoffman*), Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

[9]Prevention Program, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, MD.

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[*]*Reprint requests to:* Gerald Clamon, MD, Department of Internal Medicine, University of Iowa Hospitals, Iowa City, IA 52242.

tients with previously untreated SCCL were randomized to receive or not receive 28 days of IVH at the initiation of their antineoplastic therapy. Patients were stratified by extent of disease, prior weight loss, and performance score. Patients receiving IVH were given caloric and protein replacement based on their nutritional status at entry in the study. Further caloric and protein intake was escalated to assure adequate replenishment. Intensive chemotherapy using a five-drug regimen with chest irradiation for patients with limited disease and prophylactic cranial irradiation in responders was given.

We report here on the (*a*) survival and response to antineoplastic therapy in IVH versus control patients, (*b*) effects of IVH on patients with varying degrees of weight loss, (*c*) effects of IVH on the tolerance of delivered chemotherapy, (*d*) effects of IVH on survival by days of IVH received, and (*e*) effects of IVH on infectious complications during granulocytopenia caused by chemotherapy.

METHODS

Eligibility Criteria

All patients had histologically or cytologically documented SCCL. Pathology was reviewed by a reference pathologist (Dr. Mary Matthews, National Cancer Institute). Patients were required to have had no prior therapy, a performance score of 3 or better (Eastern Cooperative Oncology Group [ECOG] scale),[11] and measurable or evaluable disease. Patients were excluded with superior vena cava obstruction, hyponatremia ($Na < 125$ mEq/L), or CNS metastases for whom IVH was felt to be an unacceptable risk. Patients with cardiac disease precluding doxorubicin therapy were also excluded. Other requirements were wbc count $\geq 3000/mm^3$, platelet count $\geq 100{,}000/mm^3$, bilirubin < 2 mg/dl, serum creatinine < 2 mg/dl, and BUN < 30 mg/dl.

Patients were accrued from the University of Iowa, University of California-Irvine, University of Florida, University of Toronto, and New York University. The protocol was reviewed by the Human Ethics Committee of the participating hospitals and all patients gave written informed consent.

Staging and Nutritional Assessment

Patients were staged as having limited versus extensive disease on the basis of physical examination, chest x-ray, liver and bone scans, radionuclide or computerized tomographic brain scan, and bone marrow aspirate and biopsy. Patients with disease confined to one hemithorax and the ipsilateral supraclavicular lymph nodes were considered to have limited disease. Further spread (including pleural effusion) was defined as extensive disease.

Nutritional assessment consisted of history of weight loss over the 6 months prior to diagnosis and measurement of height, weight, mid-arm muscle circumference, triceps skin fold, serum albumin, total iron-binding capacity (TIBC), serum protein, and creatinine height index. Nutritional status was evaluated prior to treatment and repeated every 3 weeks. Normal nutritional status was defined as $< 2\%$ weight loss prior to diagnosis, TIBC > 270 mg/dl, albumin > 3.4 mg/dl, anthropometric measurements within 80% of predicted, creatinine-height index within 90% of predicted for height and sex, and urine urea nitrogen < 12 g/24 hours.

Study Design

For randomization, patients were stratified by limited versus extensive disease, ECOG performance score 0, 1 versus 2 versus 3, and weight loss $< 2\%$ versus weight loss $> 2\%$. The 2% cut off was based on an earlier study showing this level to be significant (1). The study randomization was through a central office and blocked so that the number of patients in each treatment group would be approximately equal in each hospital. Patients randomized to receive IVH received a silastic, Hickman, Broviac, or polyethylene subclavian catheter. Standard catheter maintenance techniques were employed. Febrile episodes were evaluated by a protocol (*see* below). IVH was started 7 days prior to the first dose of chemotherapy and continued for a total of 28 days unless complications occurred. In patients not receiving IVH, chemotherapy was started immediately. Thereafter, the two groups continued on the same program of antineoplastic therapy.

Nutritional Therapy

IVH was provided as an amino acid mixture (4.25% of Travesol), hypertonic glucose, and lipid emulsion (10%). Nonprotein calories were evenly divided between glucose and lipid. Electrolytes, multivitamins, trace elements, folate, and vitamins K and B12 were added. Patients with normal nutritional status at randomization were started at 32 calories/kg/day and 1.0 g/kg/day of protein. After 1 week, these patients were increased to 40 calories/kg/day and 1.25 g/kg/day of protein and maintained at this level for 3 weeks. Nutritionally depleted patients were started at 48 calories/kg/day and 1.5 g/kg/day of protein. After 1 week, these patients were escalated to 56 calories/kg/day and 1.75 g/kg/day of protein. Patients at the University of Toronto received no oral intake while receiving IVH, while patients at all other institutions were allowed to eat ad libitum. At the end of IVH, the glucose was gradually tapered and the patients weaned

[11] ECOG scale: 0 = asymptomatic; 1 = symptomatic; 2 = bedridden $< 50\%$ of time; 3 = bedridden $> 50\%$ of time; and 4 = bedridden 100% of time.

from IVH over 24–48 hours. The amount of IVH received was recorded and compared to the amount specified by the protocol. Nutritional assessment was repeated weekly during IVH.

Treatment

All patients received induction chemotherapy (CAV′) consisting of high-dose cyclophosphamide (1200 mg/m^2), doxorubicin (70 mg/m^2), and vincristine (2 mg for two cycles) 3 weeks apart. Unless allergic, patients were given prophylactic trimethoprim-sulfamethoxazole from Days 8 to 18 during each cycle of CAV′.

At 6 weeks, responders were given two cycles of cyclophosphamide (1000 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (2 mg) (CAV). Prophylactic cranial irradiation (2000 rads in five fractions) was given to responders after the second CAV dose. Partial responders with limited disease were given chest radiotherapy (2500 rads in ten fractions) over 2 weeks. After two cycles of CAV, therapy was switched to etoposide (100 mg/m^2 iv daily for 3 days), methotrexate (50 mg/m^2 iv on Day 1), and oral leucovorin (5 mg/m^2 every 6 hours for six doses beginning 36 hours following methotrexate). Five cycles of etoposide and methotrexate were given at 3-week intervals. Treatment was then crossed back to CAV until the cumulative dose of doxorubicin reached 450 mg/m^2. Five additional cycles of etoposide and methotrexate were then given to complete approximately 1 year of therapy. At any point after the first two cycles, nonresponders or patients with progression were crossed to the alternate regimen. Doses of all regimens were adjusted to nadir and day of treatment granulocyte and platelet counts. Doses were also adjusted for severe mucositis. All radiotherapy fields and dosimetry were reviewed by a reference radiotherapy center at the University of Toronto.

Management of Febrile Episodes

Patients with a temperature > 38.5°C or two oral temperatures of > 38.2°C, < 4 hours apart with no explanation, such as recent transfusion, were defined as febrile. Patients were considered granulocytopenic if the granulocyte count was < 1000/μl. Evaluation of fever included chest x-ray and cultures of throat, sputum, blood (aerobic, anaerobic, and fungal), urine, and any other appropriate sites. For temperatures > 38.5°C in patients receiving IVH, the IVH bottle and infusion line were disconnected and cultured. Where possible, simultaneous cultures were drawn through the IVH line and a peripheral vein. If, after 48–72 hours, the fever had not dropped to < 38.5°C and repeated cultures were negative or an alternate explanation for the fever was not found, the central venous catheter was removed and the tip cultured. Iv aminoglycoside plus an antipseudomonal penicillin agent (such as Carbenicillin or Ticarcillin) or a first-generation cephalosporin (such as Cefazolin) was used to treat the febrile, neutropenic episodes.

Microbiologically documented infections were defined as infections in which a site and pathogen were defined by positive cultures from standard sites, including biopsies or convincing serologic evidence of infection. Septicemia included patients with positive blood cultures not considered to be contaminants. Pneumonitis was defined as a positive x-ray with positive cultures from blood or sputum. Catheter infection was defined as a positive blood culture at the catheter site even if positive blood cultures were not obtained at a different site.

Clinically documented infections were defined by situations in which a site of infection was found but a pathogen was not identified. This included evidence of pneumonitis, cellulitis, or other soft tissue infections from which an organism was not isolated.

Dietary Records

Each patient was asked to keep a 3-day diet record prior to the initiation of treatment; at the end of 3 weeks after the first, second, fourth, eighth, and 12th cycles of chemotherapy; and at the end of 1 year. Each diet record was reviewed with a dietician for completeness, quantitation, and accuracy the day following its collection. At baseline, 31 patients unable to provide an accurate 3-day record (due to interference with diet by staging procedures or due to the need to start therapy immediately) provided a 24-hour diet recall. Basal energy expenditure (BEE) estimates for each patient were calculated using the Harris-Benedict equation (14). Adequate caloric intake was defined as > 1.2 × BEE (15). Adequate protein intake was defined as > 0.8 g/kg/day (16).

Evaluation of Response

Complete response was defined as the clinical disappearance of all evidence of tumor on chest x-ray, scans, and bone films. Histologic complete response included a negative repeat bronchoscopy and repeat biopsies of areas previously positive at diagnosis. Partial response was defined as a decrease of > 50% in the product of cross-sectional diameters of measurable lesions lasting at least 3 weeks. Disease progression was defined as the appearance of any new lesions or a 25% increase in the product of cross-sectional diameters of indicator lesions. Stable disease was defined as changes less than disease progression or partial response.

Statistical Methods

Survival curves were calculated from the day of randomization to the date of death or the most recent follow-up, using the product limit method of Kaplan and Meier (17). Death from any cause was considered to be a failure.

Patients were analyzed in the treatment group to which they were randomized. Immediately prior to statistical analysis, all patient survival times, response data, etc, were reviewed for accuracy and updated to reflect the most current data. The Mantel test (18) was used to compare two or more survival curves, and the trend test of Tarone (19) was used to evaluate survival curves when the factor used to define the curves had a natural ordering. The life-table regression approach of Cox (20) was used to evaluate the importance of several factors simultaneously. The Pearson chi-square test was used for the evaluation of contingency tables and corrected for continuity where appropriate. All P values in this report are of the two-sided type.

RESULTS

Of the 128 patients randomized in the study, 119 had SCCL on review of the pathologic material. Eight patients were ineligible based on pathology alone and one patient was ineligible based on failure to meet multiple on-study requirements. These 119 patients are considered evaluable for this trial and form the basis of this report. Median time from entry in the study to date of analysis for all patients is > 31 months. Table 1 gives the distribution of the pretreatment patient characteristics between the two treatment groups and demonstrates the similarity of each group with respect to these factors.

The efficacy of the therapy employed is reflected by an overall response rate of 93% and a complete response rate of 46%. Patients with limited disease had a median survival of approximately 18 months and patients with extensive disease had a median survival of approximately 11 months (P = 0.002) (fig 1). Ninety-seven of the 119 evaluable patients had died, with 17 of 51 limited-disease patients and five of 68 extensive-disease patients still surviving; median follow-up was 31 months.

Too few patients were in advanced performance score categories 2 and 3 compared to patients in score categories 0, 1 to meaningfully evaluate the prognostic significance of this variable. Survival was not altered by the sex of the patient (P = 0.83). Patients with two or more abnormal liver function tests (bilirubin, SGOT, and alkaline phosphatase) and without other medical explanation for their cause were grouped with patients with liver radionuclide scans showing metastatic disease and/or positive liver biopsy for the purposes of analysis. Such patients defined to have liver involvement had a median survival of 10 months, significantly shorter survival than the median survival of 18 months in patients without such involvement (P < 0.001). This significant survival difference remains when only patients with extensive disease were analyzed (P = 0.001).

Response rates and survival were not significantly altered by IVH. Complete responses were noted in 48% of IVH patients versus 43% of control patients (table 2). The administration of IVH did not alter the survival of these patients with SCCL (fig 2). The survival plots of IVH versus control patients virtually overlap (P = 0.78). In addition, survival did not differ significantly between the IVH and control patients after adjusting separately for each of the following factors using the Cox model: disease extent (limited vs extensive; P = 0.58), pretreatment weight loss (< 5% vs > 5%; P = 0.76), liver involvement (presence vs absence; P = 0.69), sex (P = 0.79), or age (≤ 60 vs > 60; P = 0.94).

As weight loss at the time of diagnosis increased, there was a significant trend for the patients to have a shorter survival period (P = 0.05; trend test of Tarone) (fig 3). For patients with > 10% weight loss over the 3 months prior to diagnosis, median survival was approximately 290 days; median survival was approximately 500 days in patients who had gained weight over the 3 months prior to randomization. A univariate Cox regression

TABLE 1.—Patient characteristics*

Characteristic	IVH	No IVH	Total
Total	57	62	119
Sex			
Male	41	48	89 (75)
Female	16	14	30 (25)
Disease extent			
Limited	22 (39)	29 (47)	51 (43)
Extensive	35 (61)	33 (53)	68 (57)
Weight loss			
< 2%	25 (44)	28 (45)	53 (45)
> 2%	32 (56)	34 (55)	66 (55)
ECOG performance score			
0, 1	52 (91)	52 (84)	104 (87)
2	3 (5)	7 (11)	10 (8)
3	2 (4)	3 (5)	5 (4)
Mean age in yrs (range)	59 (38-75)	61 (41-77)	60 (38-77)

* Unless otherwise specified, values = No. of patients (%).

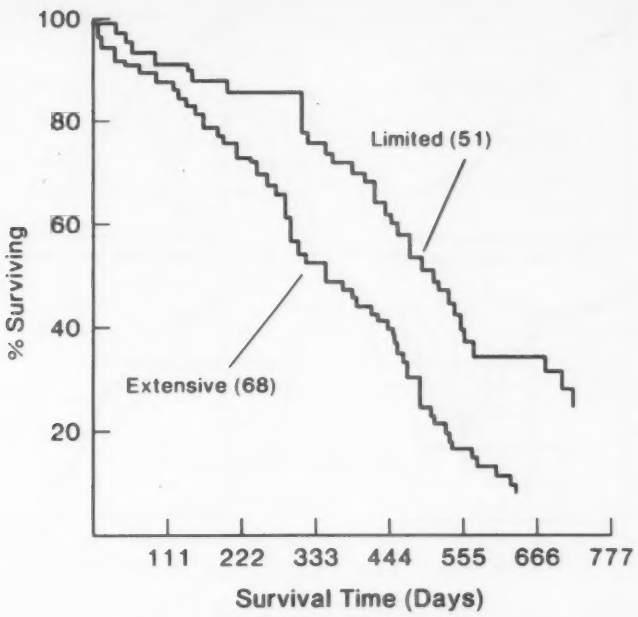

FIGURE 1.—Survival for disease extent (limited vs extensive).

model using the actual percent weight loss value also showed percent weight loss to be significantly related to survival ($P = 0.003$). However, the association between percent weight loss and survival was not significant after adjusting for disease extent ($P = 0.45$). Nutritional variables other than weight loss were not significantly associated with survival when compared by categorizing serum albumin, caloric intake, protein intake, triceps skinfold, or TIBC values as shown in table 3. Similar nonsignificant univariate results were obtained using the actual values of each parameter in conjunction with the Cox regression model. Not surprisingly, there was no significant relation of each factor to survival after adjusting for disease extent.

Based on previous conjecture that IVH might have led to benefit only in patients with adverse nutritional status at entry in the study, these patients were separately evaluated. As seen in figure 2, patients with a > 5% weight loss did not benefit from IVH. Survival of IVH and control patients was compared in four analyses for patients with (*a*) baseline albumin less than the median of the group, (*b*) pretherapy caloric intake < 1.2 × BEE, (*c*) pretherapy protein intake < 0.8 g/kg/day, and (*d*) TIBC less than lower limits of institution's normal range. IVH did not prolong survival in any of these groups relative to control ($P = 0.56$, 0.33, 0.89, and 0.84, respectively) (fig 4). However, these analyses were based on small numbers of patients and the power is low to detect moderate differences even if they did indeed exist.

There was a significant difference in caloric intake and protein intake during the IVH administration between treated and control patients. Just prior to Cycle 2 of chemotherapy, patients receiving IVH had a caloric intake of 2.37 times their basal energy expenditure/day as compared with 1.30 kcals/BEE/day for control patients ($P = 0.0001$). Protein intake was similarly increased in

TABLE 2.—Response: IVH vs controls*

Response	IVH	Controls	Total†	*P* value‡
Complete	24 (48)	26 (43)	50 (46)	> 0.95
Partial	20 (40)	32 (53)	52 (47)	
Other	6 (12)	2 (4)	8 (7.2)	

* Unless otherwise specified, values = No. of patients (%).

†Nine patients were inevaluable for response since they either died before receiving any dose of chemotherapy or their survival was < 3 wks.

‡Kruskal-Wallis test for ordered response adjusted for ties.

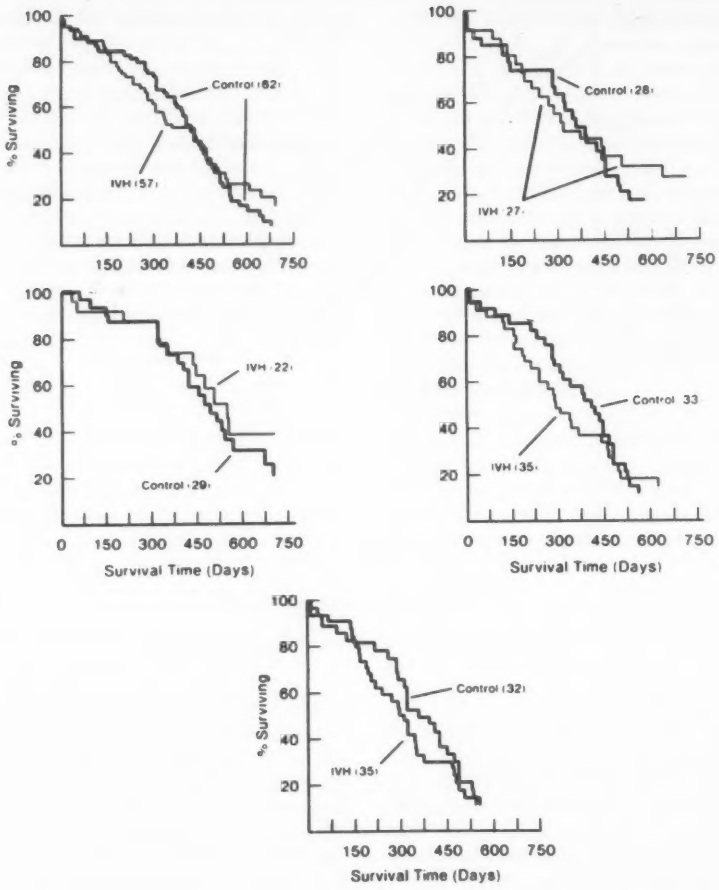

FIGURE 2.—Survival for treatment group (IVH vs control). Upper left = survival in all patients, IVH vs control. Log-rank, 0.76 (P = 0.7832). Lower left = survival in patients with only limited disease, IVH vs control (P = 0.56). Upper right = survival in patients with pretreatment weight loss > 5%, IVH vs control (P = 0.30). Lower right = survival in patients with only extensive disease, IVH vs control (P = 0.79). Bottom = survival in patients with liver involvement, IVH vs control (P = 0.65).

patients receiving IVH (1.70 g/kg/day of protein) versus those not receiving IVH (1.12 g/kg/day of protein) (P = 0.0001). At this point in the treatment program, IVH patients had achieved a 5% weight gain versus a 3% weight loss for control patients (P = 0.0001). Detailed reports on the nutritional and dietary intake of these patients have been separately prepared.

The effect of IVH on the amount of chemotherapy able to be given was assessed by calculating the actual doses given per meter squared for the initial three cycles of treatment for IVH and non-IVH patients. The actual doses administered did not differ in any of the three cycles except Cycle 1. In Cycle 1, a difference in doxorubicin dose occurred which is < 1 mg/m^2 and is not clinically significant. In table 4, total treatment delays and delays due to hematologic toxicity are detailed. In the second cycle during the IVH administration, there is a tendency toward less frequent overall delays in those patients receiving IVH (P = 0.07). If the total dose received in milligrams per meter squared is also corrected by the number of days per cycle, patients on IVH received more chemotherapy. However, the differences in doses expressed in milligrams per meter squared per day, while statistically different, vary by < 5 mg/m^2/day of cyclophosphamide or doxorubicin and may not be clinically significant.

During the IVH, complications arose necessitating temporary (19 patients) or permanent (16 patients) discontinuation of the parenteral nutrition. Twenty-two pa-

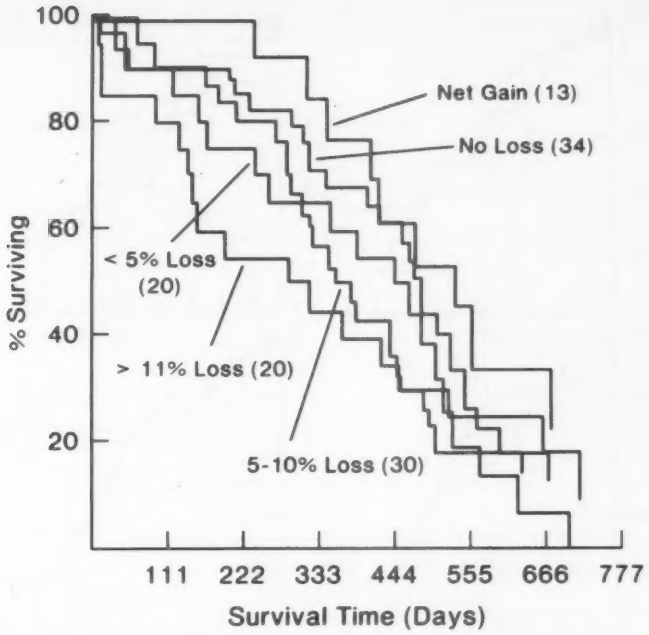

FIGURE 3.—Survival by weight change over the 3 mos prior to randomization.

tients received IVH without interruption; including patients with temporary interruptions, 41 of 57 (72%) finished the IVH. The durations of interruptions were generally short so that seven of 19 patients with interruptions still received 28 days of IVH; the median number of days of IVH received in the interrupted group was 26 days. Details of the toxicity of IVH will be reported separately. Patients requiring permanent discontinuation of IVH received a median of only 7 days of IVH. Six of these patients had severe cardiac or respiratory complications and two had severe hemoptysis. For patients who were alive 28 days from the time of randomization, there was no difference in survival for those receiving 8–27 days of IVH versus the full 28 days of IVH. Patients receiving 0–7 days of IVH fared worse than the other two groups. This finding is not of clinical importance, since the number of such patients is small and other clinical characteristics plausibly explain the short survival. If corrected for extent of disease, the length of IVH given did not have a significant correlation with survival (fig 5).

As presented in the Methods section, the highest doses of chemotherapy were given in the first two cycles when patients were receiving IVH. This intensive therapy resulted in a median granulocyte count nadir of 600/mm^3 in patients receiving IVH and 350/mm^3 in patients not receiving IVH. However, this difference in nadir counts did not translate into protection from fever in the IVH group. During the first cycle, 23 of the 57 patients randomized to IVH had 28 episodes of fever as compared with only eight patients, each being febrile only once, among the 62 patients not receiving IVH. This difference

TABLE 3.—Effects of serum albumin, caloric intake, protein intake, triceps skinfold thickness, and TIBC on survival

Factors	Log-rank *P* value
Serum albumin < group median*	
vs	0.77
Serum albumin ≥ group median	
Caloric intake < 1.2 calories/BEE/day*	
vs	0.37
Caloric intake ≥ 1.2 calories/BEE/day	
Protein intake < 0.8 mg/kg/day	
vs	0.87
Protein intake ≥ 0.8 mg/kg/day	
TIBC < lower limits of institution normal range	
vs	0.76
TIBC ≥ lower limits of institution normal range	
Triceps skinfold ≤ 11 for males or ≤ 22 for females	
vs	0.87
Triceps skinfold > 11 for males or > 22 for females	

* Use of serum albumin cut-point of 3.5 mg/dl and a caloric intake cut-point of 0.1 calorie/BEE/day provided similar nonsignificant survival differences ($P = 0.43$ and $P = 0.51$, respectively).

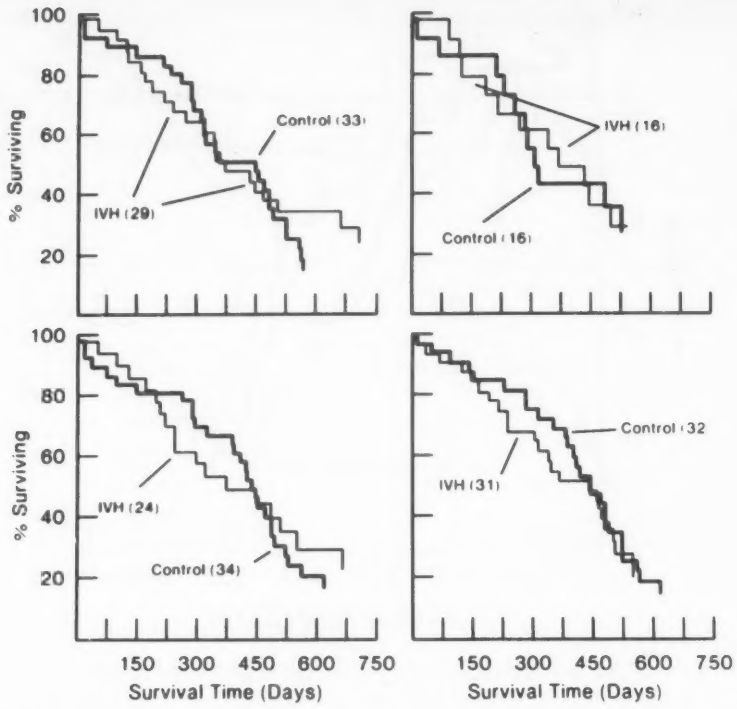

FIGURE 4.—Survival by baseline nutritional status. Upper left = survival in patients with baseline albumin < 3.4 g/dl, IVH vs control ($P = 0.56$). Lower left = survival in patients with caloric intake < 1.2 × BEE, IVH vs control ($P = 0.33$). Upper right = survival in patients with protein intake < 0.8 g/kg/day, IVH vs control ($P = 0.89$). Lower right = survival in patients with TIBC less than normal, IVH vs control ($P = 0.84$).

is highly significant ($P < 0.001$).

Analysis of the etiology of the febrile episodes also reveals differences between the groups. During Cycle 1, only eight of 28 (29%) febrile episodes occurred in patients receiving IVH who were granulocytopenic at the onset of their fever as opposed to six of eight (75%) febrile episodes which occurred in patients not receiving IVH who were granulocytopenic ($P = 0.05$). The increase in febrile episodes in IVH patients was usually not associated with granulocytopenia. Of the 28 febrile episodes in patients receiving IVH, eight were undefined in origin. In the control patients, five of eight febrile episodes were undefined in origin. The sites of infection and their occurrence with respect to granulocytopenia are listed in table 5. In the nine episodes of catheter-related sepsis, eight occurred in granulocytopenic patients. Thus, the predominant infections in the IVH group were either catheter-related or pneumonia not related to granulocytopenia. After Cycle 1, there was no significant difference in febrile or infectious episodes between the groups.

TABLE 4.—Treatment delays

	IVH		No IVH		
	No. of patients with delay	Total No. of patients (%)	No. of patients with delay	Total No. of patients (%)	*P* value
			All delays		
Cycle 2	1	50 (2)	8	58 (14)	0.07
Cycle 3	6	49 (12)	12	57 (21)	0.37
			Delays due to myelosuppression		
Cycle 2	0	1 (0)	5	8 (63)	> 0.90
Cycle 3	1	6 (17)	5	12 (42)	0.62

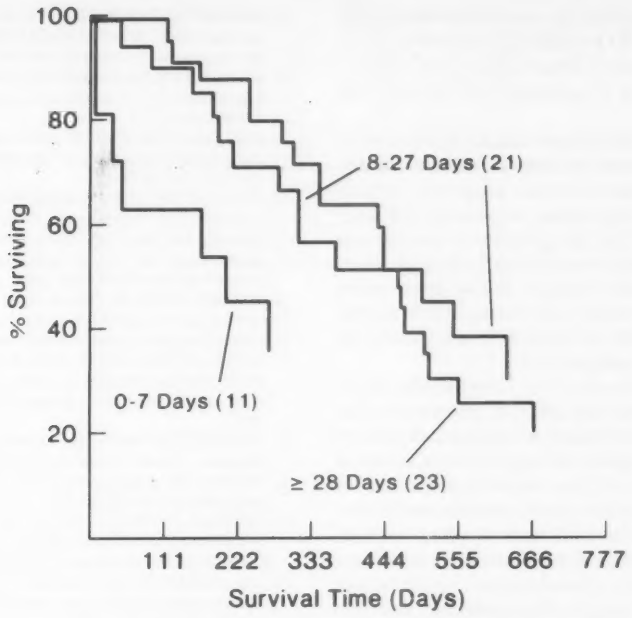

FIGURE 5.—Survival by No. of days of IVH completed.

DISCUSSION

In this randomized study of 119 patients, no significant benefit for IVH could be identified in terms of survival, response to therapy, amelioration of toxicity, or ability to deliver chemotherapy. Based on the observed differences in survival between the two treatment groups, confidence interval calculations also showed that any possible true treatment differences in survival must be small. It is unlikely that a significant IVH survival benefit could have been missed in this study. Infectious complications and catheter complications were more frequent in the IVH group. Our study failed to demonstrate benefit in any subgroup of patients. More profound weight loss at diagnosis, nutritional inadequacy at diagnosis (decreased caloric intake, low albumin, and low TIBC), and more extensive disease failed to identify a subgroup benefited by the administration of IVH.

The role of IVH as an adjuvant to antineoplastic therapy is not defined at this time. Studies showing improvement in response, survival, or amelioration of toxicity have been reported for patients receiving IVH in smaller clinical trials (3-5,21). Other randomized trials have failed to establish benefit (6-8) and some investigators have suggested that only selected patients would benefit (9,10). These studies have involved < 50 patients and re-

TABLE 5.—Etiology of febrile episodes during Cycle 1 of therapy

	No. of febrile episodes*			No. of infectious episodes*		
	G+	G-	Total	G+	G-	Total
Pneumonia	2	7	9	1	2	3
Urinary tract infection	0	0	0	0	0	0
Sepsis	1	0	1	0	0	0
Catheter-related sepsis	1	8	9	0	0	0
Other	1	0	1	0	0	0
Origin undefined	3	5	8	5	0	5

* G+ = granulocytopenia, defined as neutrophil count ≥ 1000 cells/mm^3. G- = no granulocytopenia, defined as neutrophil count < 1000 cells/mm^3.

sults based on subgroup analysis could not be definitively interpreted. Our study of considerably greater numbers of patients fails to identify a subgroup for whom 28 days of IVH at the initiation of antineoplastic therapy is of benefit.

Our study does not demonstrate that all adjunctive nutritional therapy for cancer patients is fruitless. Cancer-induced weight loss remains a major prognostic variable and anorexia remains distressing to patients and their families. Four-week IVH at the initiation of therapy was unable to sustain the patient nutritionally through 1 year of intensive antineoplastic therapy. In a separate report we will detail how the weight gain during IVH is quickly dissipated so that by 12–15 weeks IVH and control patients are nutritionally comparable.

The implications of this study for future studies of adjuvant nutritional therapy are multiple. Avenues for further investigation should include (*a*) randomized trials of long-term nutritional support lasting the entire period of antineoplastic therapy, (*b*) more exacting definition of the nutritional aberrations in cancer patients, and (*c*) further exploration of the enteral route for long-term replacement. If total nutritional replacement is to be beneficial for cancer patients, enteral support would be less expensive, capable of longer administration, and less likely to lead to febrile complications. There are demonstrated benefits of IVH in patients whose postoperative status or total inability to be fed orally demands IVH (22,23). By contrast, there is a lack of demonstrated value of short-term IVH in patients in whom oral intake is feasible.

Adjunctive nutrition by IVH attempts to totally replenish nutrition needs. The metabolic aberration in cancer patients is likely to vary from one individual to another. Abnormalities of glucose utilization (24,25), increases in energy expenditure (26), impaired enteral absorption after therapy (27), tumor involvement of the bowel (28), and hormonal changes (29,30) have been described. Rational nutritional intervention requires studies by tumor type of these nutritional defects and design of adjunctive therapy to address these abnormalities.

This is the largest randomized trial, to date, of IVH in patients with malignancy receiving chemotherapy. Randomized studies in patients with lymphoma (7), colon cancer (11), and testicular cancer (6) have all demonstrated no survival benefit for adjunctive IVH. No nutritionally depleted subgroup in this study could be shown to benefit from IVH. Routine administration of IVH to patients with cancer-induced weight loss who are capable of enteral alimentation is not justifiable in view of its lack of efficacy in the multiple tumors reported at this time.

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Phase I Evaluation and Pharmacokinetic Study of Weekly Iv Thymidine and 5-FU in Patients With Advanced Colorectal Carcinoma[1,2]

Garrett Lynch,[3] Nancy Kemeny,[3,*] Hoo Chun,[3] Daniel Martin,[4] and Charles Young[3,5]

A phase I study of weekly iv thymidine (TdR) and 5-FU was carried out in patients with advanced colorectal carcinoma using two dosage schedules. Schedule 1 employed a 3-hour infusion of TdR (6–8 g/m²/hour) followed immediately by a bolus of 5-FU (100–200 mg/m²). Schedule 2 used a slightly larger dose of TdR (18 g/m²/hour for 1.5 hours), with 5-FU given 30 minutes after the TdR infusion was started. Myelosuppression was observed erratically at the higher doses of 5-FU. Diarrhea and severe fatigue were seen frequently with Schedule 1. CNS side effects were the dose-limiting effects for both schedules. For long-term use the maximally tolerated 5-FU doses were 100 mg/m²/week for Schedule 1 and 175 mg/m²/week for Schedule 2. In pharmacokinetic studies in five patients, both schedules produced prolonged plasma beta-half-lives of 5-FU (96–189 minutes). Extensive formation of floxuridine was seen with both schedules. It appears likely that CNS toxic effects are characteristic of TdR-containing 5-FU regimens and would limit the therapeutic potential of this approach. [Cancer Treat Rep 69:179–184, 1985]

Current approaches to cancer chemotherapy include the development of new effective agents and attempts to increase the therapeutic index of conventional drugs. The theoretical possibility exists that the therapeutic index of antimetabolites may be improved by biochemical modulation which selectively alters their metabolism. 5-FU has been the focus of much of the research in biochemical modulation because it has definite though suboptimal activity against colorectal and breast carcinomas. The antitumor activity of 5-FU has been customarily attributed to an irreversible drug-induced inhibition of thymidylate synthetase, which inhibits DNA synthesis by depletion of the thymidine (TdR) 5′-triphosphate pool (1). However, recent work has demonstrated that in some model systems tumor cell kill may be directly correlated with the incorporation of 5-FU into RNA, which can adversely affect a variety of cellular mechanisms requiring RNA processing and function (1–6).

The combined use of 5-FU with an agent capable of increasing its incorporation into RNA may increase the effectiveness of 5-FU. In a study utilizing the murine CD8F1 breast carcinoma, a weekly schedule of TdR given ½ hour before 5-FU resulted in a 70% greater tumor inhibition than did 5-FU alone (3). The synergistic antitumor effects of the combination of TdR and 5-FU have also been observed in a number of tumor systems (4,7,8). TdR might also enhance the therapeutic activity of 5-FU by causing selective reversible cytokinetic arrest by TdR "feedback" of normal cells compared with malignant cells (6,9). It may also protect 5-FU from catabolic degradation, since TdR is catabolized by the same pathway as 5-FU (7,10,11).

Woodcock et al (12) carried out a phase I evaluation which employed a monthly schedule of 15 g of TdR followed by a bolus of either 7.5 or 10.0 mg/kg of 5-FU. The dose-limiting toxic effect was myelosuppression. Neurotoxicity, both cerebellar and cerebral, was occasionally noted. Pharmacologic studies demonstrated that prior treatment with TdR greatly retarded the degradation of 5-FU, thereby prolonging its plasma half-life. The studies also documented that extensive

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[3]Solid Tumor (*G. Lynch, N. Kemeny*, and *H. Chun*) and Developmental Chemotherapy (*C. Young*) Services, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, NY.

[4]Department of Surgery, Catholic Medical Center, Woodhaven, NY.

[5]We thank Dr. Counce Hancock for assistance in the pharmacokinetic analyses.

[*]*Reprint requests to:* Nancy Kemeny, MD, Solid Tumor Service, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, 1275 York Ave, New York, NY 10021.

conversion of 5-FU to floxuridine (FUdR) occurs in the presence of TdR. Similar results were observed in other studies (13-15).

In this communication we report the results of a study designed to develop an acceptable *weekly* dose of TdR with 5-FU that could provide the basis for subsequent phase II trials.

MATERIALS AND METHODS

Twenty-nine patients with advanced colorectal carcinoma were entered in the protocol. Criteria for entry in the study included Karnofsky performance status $\geq 40\%$, wbc count $\geq 4000/mm^3$, platelet count $\geq 150{,}000/mm^3$, serum creatinine < 1.5 mg/100 ml, and no chemotherapy within 1 month of starting the protocol.

Each patient had an initial complete history and physical examination, chest x-ray, ECG, urinalysis, cbc, serum biochemical screening profile, serum creatinine, and carcinoembryonic antigen. Radionuclide and/or computerized transaxial tomographic scans were obtained only if clinically indicated.

Although this was a phase I study and the presence of measurable disease was not a criterion for entry, our patients were assessed for therapeutic response. Partial response was defined as a $> 50\%$ decrease in the sum of the products of the largest perpendicular diameters of measurable lesions for > 1 month; minor response was defined as a $> 25\%$ measurable decrease in tumor size; stable disease was defined as a $< 25\%$ measurable change in tumor size; and progressive disease was defined as a $> 25\%$ measurable increase in tumor size or the development of new lesions.

Of the 29 patients entered, 28 were evaluable for toxicity. The median age of the evaluable patients was 59 years (range, 36-73); the median Karnofsky performance status was 80% (range, 70-100); and the median interval from diagnosis to protocol treatment was 17 months (range, 4-47). Only one patient had not had prior chemotherapy; five patients had received radiation therapy in addition to chemotherapy. Of the previously treated patients, 26 had had prior treatment with 5-FU; of these p ents, 20 had received semustine, 12 had received vincristine, and six had received streptozocin.

Measurable metastatic sites included liver (16 patients), lung (six), lymph nodes (four), and pelvic or abdominal masses (four).

Dosage Schedules

TdR was supplied in 500-ml bottles containing 15 g of TdR (30 mg/ml) by the Investigational Drug Branch, National Cancer Institute, Bethesda, MD. Two basic dosage schedules were used. Schedule 1 employed a 3-hour infusion of TdR (6-8 g/m^2/hour) followed by 5-FU (100, 150, or 200 mg/m^2 given by direct iv push at the end of the TdR infusion). The first three patients had received a regimen of TdR (8 g/m^2/hour infusion) for 3 hours, followed by 5-FU (200 mg/m^2). However, this combination caused severe toxicity. The TdR dose was subsequently reduced to 6 g/m^2/hour for 3 hours, followed by 5-FU starting at 100 mg/m^2 and escalating to 200 mg/m^2 by 50-mg/m^2 increments. Schedule 2 consisted of a TdR infusion at a dose of 18 g/m^2/hour for 1.5 hours, with 5-FU at dose levels of 100, 125, 150, and 175 mg/m^2 administered iv 30 minutes after the start of TdR infusion.

A cycle of therapy was a weekly dose × 3, with a 2-week rest period thereafter. At least three patients were entered at each given dose level and were evaluated for toxicity before patients were entered at the next higher dose. Those patients who had neither therapeutic effect nor toxicity were given another cycle at a higher dose of 5-FU. Plasma content of TdR, 5-FU, and FUdR was measured by a modification of the high-pressure liquid chromatography method described previously (12,16). Apparent half-life calculations for α- and β-half-lives were obtained from the drug concentration versus time plots by the method of residuals (17). The area under the curve (AUC) calculations were estimated by trapezoidal approximation (17).

RESULTS

Toxic Effects

Schedule 1

The original regimen of TdR at a dose of 8 g/m^2/hour infused for 3 hours followed by 5-FU at a dose of 200 mg/m^2 caused severe toxicity. Of the three patients treated with this regimen, two required admission and treatment of sepsis. The median wbc count nadir was $1700/mm^3$ (range, 300-2400). The median platelet count nadir was $72{,}000/mm^3$ (range, 68,000-210,000). Gastrointestinal toxicity occurred in all three patients treated: mild nausea and vomiting (two patients) and diarrhea (one). Neurotoxicity occurred in two of the three patients. One patient experienced only dizziness. However, the second patient developed seizures and coma; the coma lasted for 2 weeks before recovery.

The TdR dose was subsequently reduced to 6 g/m^2/hour for 3 hours, followed by 5-FU starting at 100 mg/m^2 and escalating to 200 mg/m^2 by 50-mg/m^2 increments. The toxicity of the various dose levels is outlined in table 1. With the modified schedule, myelosuppression was minimal at all doses of 5-FU. There were no gastrointestinal toxic effects at the 100-mg/m^2 dose, while at the 150-mg/m^2 dose, one patient had vomiting, one had mucositis, and two had diarrhea

TABLE 1.—Toxicity of TdR with 5-FU schedules

Dose schedule		No. of patients/ treatments	Median nadir (range)*		Change in hemoglobin (range)†	No. of patients with toxic effect/No. treated						
TdR	5-FU		Wbc count	Platelet count		Nausea and vomiting	Diarrhea	Mucositis	Fatigue	Dizziness	Ataxic gait	Others
6‡	100§	9/24	5.6 (2.5-8.5)	141 (110-216)	−0.9 (−3.7 to +1.9)	1/9	2/9	0/9	6/9	7/9	2/9	Headache (1/9); depression (1/9)
6‡	150§	4/6	5.5 (3.8-5.9)	184 (61-276)	−0.3 (−1.0 to +0.7)	1/4	2/4	1/4	1/4	3/4	3/4	
6‡	200§	6/11	5.3 (0.6-7.0)	151 (36-321)	−1.4 (−0.1 to −2.7)	3/6	3/6	0/6	5/6	4/6	1/6	Fever (1/6); headache (1/6)
8‡	200§	3/7	1.7 (0.3-2.4)	72 (68-210)	−1.0 (−0.6 to −1.8)	2/3	1/3	1/3	2/3	1/3	0/3	Sepsis (2/3); seizure and coma (1/3)
18¶	100§	3/5	5.6 (3.9-7.3)	221 (197-245)	−0.3 (−1.1 to +0.5)	0/3	2/3	0/3	2/3	2/3	0/3	
18¶	125§	3/8	6.7 (2.4-9.3)	135 (21-218)	+0.6 (−1.2 to +0.9)	0/3	1/3	0/3	0/3	2/3	0/3	Hallucination (1/3); headache (1/3); tremor (1/3)
18¶	150§	7/28	4.6 (4.1-11.1)	183 (45-575)	−0.4 (−2.6 to +2.8)	3/7	1/7	0/7	1/7	2/7	0/7	Tremor (1/7); confusion (1/7); hallucination (1/3)
18¶	175§	5/13	5.8 (3.6-7.1)	217 (122-353)	−1.0 (−1.4 to +0.3)	0/5	1/5	0/5	0/5	2/5	2/5	Headache (1/5); confusion (1/5)

* × 10^3 cells/mm^3.
†g/100 ml.
‡g/m^2/hr infusion for 3 hrs.
§mg/m^2 by iv push.
¶g/m^2/hr infusion for 1.5 hrs.

among four patients. Neurotoxicity remained a major problem and was dose-limiting. At the 100-mg/m^2 dose, seven of nine patients experienced dizziness and two of nine had ataxic gait. At the 150-mg/m^2 dose, three of four patients had dizziness and one of four had ataxic gait. In one patient, the dizziness was incapacitating and caused the patient to be bedridden.

Schedule 2

When TdR was infused at 18 g/m^2/hour for 1.5 hours, accompanied by 100 mg/m^2 of 5-FU given by iv push 30 minutes after the start of TdR infusion, three patients tolerated the treatment without serious toxicity. Subsequent patients were treated with increasing doses of 5-FU. The results are shown in table 1. With this schedule, myelosuppression was not observed, and gastrointestinal toxic effects were reduced. Neurological symptoms were increased with higher dosages; moderate to severe neurological toxicity occurred in three of five patients at the 175-mg/m^2 dose. However, severe neurological symptoms also occurred in isolated cases at lower dosage levels. Dizziness occurred with equal frequency at all levels; the other neurological symptoms increased with increasing dosages. At the 175-mg/m^2 dose, two patients experienced severe ataxic gait. Visual hallucinations, confusion, headache, and fatigue were also seen.

Therapeutic Results

Although this study was a phase I trial, we nevertheless evaluated the 26 patients with measurable disease for antitumor response. No responses were observed. Four patients had stable disease for periods of 6 weeks to 3 months. The remaining 22 patients had progressive disease. One of the two patients without measurable disease remained stable on escalating doses of therapy for 6 months.

Pharmacokinetics

The plasma contents of 5-FU, FUdR, and TdR were measured over the first 2 hours following 5-FU administration in five patients. Three patients studied received TdR at 6 g/m^2/hour for 3 hours, with 5-FU at 200 mg/m^2 (two patients) or 100 mg/m^2 (one patient) given at the conclusion of TdR infusion. In addition, two patients were studied who received TdR at 18 g/m^2/hour, with 5-FU at 100 mg/m^2 given by iv push 30 minutes after the start of TdR infusion. The plasma concentrations of 5-FU, FUdR, and TdR at 5, 10, 20, 30, 60, and 120 minutes for these patients are listed in table 2. A prolongation of the plasma half-life of 5-FU, previously observed to be 6 minutes when 5-FU was given as a single agent (12), was readily apparent in each of the TdR-treated patients. Similar observations have been reported elsewhere (12,14,15). The $AUC_{0\text{-}120\ mins}$ for TdR was significantly higher with the larger TdR dose. The $AUC_{0\text{-}120\ mins}$ for 5-FU was highest for the 200-mg/m^2 dose following 6 g/m^2/hour of TdR. If 5-FU was administered when the TdR concentration was extremely high, an extensive conversion of 5-FU to FUdR was observed. This is consistent with the published observations of Woodcock et al (12). It is probably due to the entry of 5-FU into nucleoside phosphorylase reaction (ie, pyrimidine base - dR $\rightleftharpoons$ pyrimidine base + dR-1-PO_4), with deoxyribose-1-phosphate for formation of FUdR being provided by exogenous TdR.

DISCUSSION

After obtaining impressive antitumor results in murine tumor models (3,4,9), a combination of TdR and 5-FU was introduced into clinical trials on a monthly schedule in an attempt to increase the therapeutic efficacy of 5-FU. In earlier studies partial responses were observed with this combination in patients with colon cancer, ovarian cancer, breast cancer, and non-Hodgkin's lymphoma (12,13,18). However, the therapeutic benefits were offset by enhanced myelotoxicity over that observed with 5-FU alone, that is, the addition of TdR to 5-FU changed the dose-limiting toxic effect from gastrointestinal to myelosuppression.

When given in sufficient quantity, TdR, through its conversion to thymine, blocks the degradation of 5-FU, greatly prolongs its retention in plasma, and leads to significantly enhanced incorporation of 5-FU into RNA (4,7,12). The net effect is a considerable increase in the potency of a given quantity of 5-FU. By the addition of other agents, such as methylmercaptopurine riboside and PALA, to further enhance 5-FU incorporation into tissues and to reduce drug toxicity, Martin et al (7) have achieved a clear increase in the therapeutic index of 5-FU in murine model systems as evidenced by significantly greater tumor regression at maximally tolerated doses of the drug.

The principal aim of this phase I study was to develop a weekly dosage schedule of TdR and 5-FU suitable for combining with PALA and then with methylmercaptopurine riboside. However, the weekly dosage schedule produced changes in the toxic effects of the combination of TdR and 5-FU that had not been foreseen in the initial study design. When TdR was given at a dose of 15 g/m^2 on a monthly schedule, the dose-limiting toxic effect was myelosuppression. CNS toxicity was only occasionally seen in the initial course of therapy, but became more troublesome with cumulative doses (12). Gastrointestinal toxic effects, manifested by diarrhea and oral mucositis, were uncommon and mild when present. By shifting to the weekly schedules, CNS toxicity became dose-limiting, and

TABLE 2.—Pharmacokinetic comparisons of 5-FU, FUdR, and TdR in plasma of patients receiving TdR and 5-FU

Patient No.	Drug	Plasma concentration after injection of 5-FU at (mins) — 5	10	15	30	60	120	Apparent plasma half-life (mins) t1/2α	t1/2β	$AUC_{0-120\ mins}$*
					***Schedule 1a*†**					
1	5-FU (μM)	91	67	53‡	44	37	28	6.1	139	4778
	FUdR (μM)	16	14	13‡	11	7	5			1000
	TdR (mM)	0.56	0.48	0.39‡	0.32	0.21	0.09			28.9
2	5-FU (μM)	—	59	45‡	37	31	25	—	102	3925
	FUdR (μM)	—	21	17‡	15	9	3			1175
	TdR (mM)	—	0.91	0.68+	0.59	0.36	0.21			50.2
					***Schedule 1b*†**					
3	5-FU (μM)	34	28	21	18	12	11	4.7	142	1795
	FUdR (μM)	13	14	12	11	8.2	6.8			1083
	TdR (mM)	1.0	1.1	0.9	0.8	0.6	0.3			74.3
					***Schedule 2*†**					
3	5-FU (μM)	42	23	14	10	6.4	5.0	3.3	96	1128
	FUdR (μM)	25	25	21	20	17	8.7			1936
	TdR (mM)	1.6	1.8	1.8	2.3	2.8	1.7			263.8
4	5-FU (μM)	24	12	9.3	6.0	3.7	4.0	4.4	189	694.5
	FUdR (μM)	31	23	23	17	13	8.6			1726
	TdR (mM)	3.2	2.9	3.5	4.0	3.0	1.8			344.5

* $AUC_{0-120\ mins}$ in plasma: 5-FU and FUdR in μM · mins; TdR in mM · mins.

†*Schedule 1a:* TdR at 6 $g/m^2/hr$ × 3 hrs; 5-FU at 200 mg/m^2 at end of TdR infusion. *Schedule 1b:* TdR at 6 $g/m^2/hr$ × 3 hrs; 5-FU at 100 mg/m^2 at end of TdR infusion. *Schedule 2:* TdR at 18 $g/m^2/hr$ × 1.5 hrs; 5-FU at 100 mg/m^2 at 30 mins into TdR infusion.

‡ 20-min postinjection of 5-FU.

drug-induced diarrhea became more frequent and severe. At dosages which were tolerated from the standpoint of neurotoxicity, myelosuppression was not consistently produced.

CNS toxicity from 5-FU is a well-established clinical entity (19,20); although not documented in humans, its physiological causation has been commonly attributed to formation of fluorocitrate and fluoroacetate, with resultant inhibition of brain cell respiration (19-21). 5-FU neurotoxicity is increased with high intermittent dosage schedule. Presumably, the high peak plasma level may produce a greater entry of 5-FU into the CNS.

Serum creatinine levels were evaluated in an attempt to determine if renal function affected the degree of neurotoxicity experienced. At each dose level, there was no difference in neurological toxicity observed, regardless of the serum creatinine values. The patient who had seizures and coma had a serum creatinine of 1.5 mg/100 ml; however, this patient also received 5-FU at 200 mg/m^2 (the highest 5-FU dose used in this study).

This study indicates that the physiologic effects produced by the combined use of TdR and 5-FU are extremely complex. A weekly dose of 5-FU (150 mg/m^2) given 30 minutes after the start of TdR infusion (18 g/m^2/hour for 1.5 hours) is a tolerable schedule from the point of view of bone marrow, gastrointestinal, and CNS toxic effects. The maximally tolerated myelotoxic dose has not been reached in this schedule because neurotoxicity prevented further escalation of the 5-FU dose. Although it would be a reasonable point from which further refinements could be initiated with the addition of other modulating drugs, it appears likely that CNS effects will continue to be troublesome in TdR-containing 5-FU regimens.

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Phase II Trial of High-Dose Recombinant Leukocyte Alpha-2 Interferon for Metastatic Colorectal Cancer Without Previous Systemic Treatment[1]

Alexander M. Eggermont,* Willem Weimar, Richard L. Marquet, Johannes D. Laméris, and Johannes Jeekel[2]

Ten patients with metastatic colorectal cancer after resection of the primary tumor were treated with high-dose recombinant leukocyte alpha-2 interferon. For a period of 12 weeks the patients received up to 20 × 10^6 IU/m^2 im twice weekly. Follow-up varied from 6 to 11 months after stopping treatment. All ten patients were evaluable for tumor response and toxicity. There was one partial response. Nine patients showed growth of metastatic marker lesions. Only three of these patients qualified as having progressive disease (> 25% increase in tumor mass). The response rate was 10%, with a 95% confidence interval of 0.3%–44.5%. Toxicity proved considerable and consisted of flu-like symptoms, fatigue, anorexia, and weight loss. Fatigue was the single most important dose-limiting factor. There were no drug-related deaths. Three patients died 3, 5, and 7 months after stopping treatment. Median survival was 18 months. [Cancer Treat Rep 69:185–187, 1985]

Interferons (IFN) are proteins and glycoproteins with antiviral, antiproliferative, and immunomodulatory activity. Among the group of solid malignant tumors IFN-induced tumor regression has been demonstrated in metastatic breast cancer (1,2), renal cell carcinoma (3), and malignant melanoma when IFN was used in combination with cimetidine (4). We studied the effect of high-dose alpha-2 rIFN given twice weekly to patients with metastatic colorectal cancer after resection of the primary tumor without previous systemic treatment.

PATIENTS, MATERIALS, AND METHODS

Between November 1982 and February 1983, ten patients with histologically confirmed metastatic lesions were entered in the study. Patients could not have proven brain metastasis, other malignant disease, or previous or concurrent chemotherapy, immunotherapy, or radiotherapy. Other entry criteria included: age < 80 years, Karnofsky index > 70%, bilirubin < 20 mmols/L, creatinine clearance > 50 ml/minute, no uncontrolled infections, no symptomatic cardiovascular disease, wbc count > 3.1 × 10^9/L, and no nonsteroid anti-inflammatory therapy. Treatment with interferon was not started earlier than 4 weeks after surgery.

Recombinant leukocyte alpha-2 IFN (Hoffmann-La Roche Inc IFL-A, Ro-22-8181) was used. The material was purified up to at least 96% homogeneity and was free of detectable endotoxin when checked with the limulus test.

Patients received up to 20 × 10^6 IU/m^2 im of alpha-2 rIFN twice weekly for a period of 12 weeks on an outpatient basis. Measurements of the marker lesions were taken every 6 weeks by means of computerized tomography and ultrasound. The usual response categories were used. Complete response was defined as the disappearance of all evidence of disease lasting a minimum of 6 weeks; partial response (PR) was defined as a > 50% decrease in the sum of the product of diameters of marker lesions, lasting a minimum of 6 weeks, without the appearance of new lesions or the growth of old lesions; progressive disease was defined as an increase of > 25% in the diameters of marker lesions and/or the appearance of new lesions; and stable disease was defined as failure to qualify for complete response, PR, or progressive disease. Patients receiving more than eight doses of alpha-2 rIFN were considered evaluable. Patient characteristics are shown in table 1.

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[2]Departments of Surgery (*A. M. Eggermont* and *R. L. Marquet*), Internal Medicine (*W. Weimar*), and Radiology (*J. D. Laméris*), Academic Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands.

* *Reprint requests to:* Dr. Alexander M. Eggermont, Department of Surgery, Academic Hospital Rotterdam-Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	10
Evaluable	10
Median age in yrs (range): 61.5 (39–76)	
Sex	
Male	6
Female	4
Median performance status (range)	
At start: 100%	
At end: 70% (40%–80%)	
6 wks after treatment: 80 (40%–100%)	
Sites of measurable disease	
Liver	9
Lung	2
Retroperitoneum	3
Carcinosis peritonei	1
Supraclavicular lymph nodes	1
Toxicity	
Flu-like symptoms	10
Weight loss	
None	4
Mild	2
Moderate	1
Severe	2
Anorexia	8
Nausea	3
Fatigue	
Mild	3
Moderate	3
Severe	4
Numb fingers (½–2 hrs)	6
Bitter taste	8
Hallucinations	3
Herpetic lesions	3
Alopecia (mild)	3
Hematologic	
Hemoglobin (mmols/L)	
> 7.5	8
< 7.5	2
Wbc count (cells/mm^3)	
> 4000	7
3000–4000	3
1500–3000	0
Platelet count (cells/mm^3)	
> 150,000	9
100,000–150,000	1
50,000–100,000	0
Hepatic	0
Renal	1

RESULTS

All patients were evaluable for tumor response and toxicity. Nine patients showed growth of metastatic marker lesions throughout the course of treatment. Only three of these patients qualified as having progressive disease. Follow-up ranged from 5 to 11 months after stopping treatment.

One patient achieved a PR at 12 weeks after starting treatment. The administration of IFN had to be discontinued at that point because of severe fatigue and malaise. The patient achieving PR, however, progressed to a near total remission (> 90% tumor reduction) during the following 4 months. During this period his general condition was excellent and previously severely disturbed liver functions became normal. Seven months after stopping treatment progressive disease compared to the near total remission state was demonstrated by computerized tomography and ultrasound of the liver. With one remission among ten patients the response rate in this trial was 10%, with a 95% confidence interval of 0.3%–44.5%.

Toxicity for this high-dose schedule proved considerable (table 1). In one patient treatment had to be stopped after eight doses because of obstructive jaundice caused by progressive disease. In one patient treatment was stopped after 14 doses because of fatigue, weight loss, and rapidly progressive disease. In two patients treatment was stopped after 16 and 20 doses because of continuous fever, disorientation, and hallucinations. The other six patients completed the course of 24 doses. In four of these patients dose reduction was necessary after 16 doses because of fatigue. Flu-like symptoms with fever up to 104°F with chills, fatigue, anorexia, and bitter taste were the most consistent side effects. Weight loss occurred in seven patients (median, 4.5 kg; range, 1–10). Six patients complained of numb fingers, which normally occurred during chills about 2 hours after the injections. No objective neurotoxic side effects or permanent sequelae could be registered by a consultant neurologist at the end of treatment of all patients. Three patients had short episodes of hallucinations, which disappeared after dose reduction or after stopping treatment. Three patients had herpetic lesions of the lips during the first week of treatment. The eruptions disappeared while continuing treatment. Mild diffuse alopecia developed toward the end of treatment in three patients and lasted for about 6 weeks. Virtually no hematologic toxicity was seen. One patient developed proteinuria, which disappeared after stopping treatment. There were no drug-related deaths. Three patients died 3, 5, and 7 months after stopping treatment. Median survival was 18 months.

DISCUSSION

Recombinant alpha-2 IFN treatment, when administered at a dose of 20×10^6 IU/m^2 im twice weekly, caused more frequent and severe side effects than expected. The toxicity is comparable to that of chemotherapy. Paresthesias, taste disturbances, and hallucinations suggest a certain degree of neural involvement, although no objective

signs of damage could be revealed by neurological examination. The classical inhibitory effect of IFN on virus replication seems to be "overruled" by nonantiviral effects at the high doses used, since three patients developed herpes hominis lesions. A PR was found in one patient, which indicates a response rate comparable to the 10%–15% tumor response that can be induced by 5-FU (5). Our results are in agreement with Neefe et al (6), who reported one PR among 18 patients treated with the same alpha-2 rIFN preparation for previously untreated advanced colorectal cancer. Studies with low-dose natural alpha-IFN (7), low-dose lymphoblastoid IFN (8), and another recombinant alpha-2 IFN preparation given in large doses (9) were not able to demonstrate antitumor effects in this disease. In six of our patients growth of the metastatic marker lesions was so slow that they failed to qualify for having progressive disease. Although this very slow progression may reflect the natural course of disease in these patients, it raises the possibility of IFN treatment having exerted a minor inhibitory effect on tumor growth. Three patients showed rapidly progressive disease.

With only one remission among ten patients, alpha-2 rIFN treatment appeared to be ineffective against metastatic colorectal cancer. Considering the high toxicity and the poor response rate of the treatment schedule as used, we decided to stop the trial after entry of ten patients.

In view of the overwhelming number of tumor cells present in measurable metastatic colorectal cancer, even the occurrence of only one PR is remarkable. Even though the mode of action by which IFN exerts an antitumor effect in vivo is still unclear, it is more likely that IFN therapy will be more effective when fewer tumor cells are present than in the situation of advanced metastatic disease. However, in view of the clinical results obtained so far, the use of alpha-2 rIFN in an adjuvant setting does not seem justified in the treatment of colorectal cancer.

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Phase II Trial of Cyclophosphamide, Doxorubicin, and Cisplatin (CAP) Versus Amsacrine in Patients With Transitional Cell Carcinoma of the Urinary Bladder: A Southwest Oncology Group Study[1,2]

Muhyi Al-Sarraf,[3] Jess Frank,[4] Joseph A. Smith, Jr,[5] Robert M. O'Bryan,[6] John J. Costanzi,[7] Ronald L. Stephens,[8] Juan Caraveo,[9] and E. David Crawford[10,*]

The combination of cyclophosphamide, doxorubicin, and cisplatin (CAP) was reported to be effective in patients with metastatic transitional cell cancer of the urinary bladder. This study was designed to test the effectiveness of the phase II agent amsacrine (*m*-AMSA) versus CAP in patients previously untreated with systemic chemotherapy, with crossover if no response occurred or at the time of progression. In 23 patients who were randomized to receive CAP, three achieved complete response, seven achieved partial response, six had stable disease, and seven had disease progression. The responses in the 22 patients who received *m*-AMSA were: one with complete response, three with partial response, six with stable disease, and 12 with progressive disease. The overall response rate to initial CAP therapy was 43% compared to 19% for initial *m*-AMSA therapy. The median duration of response to CAP was 28 weeks and to *m*-AMSA was 21 weeks. There were no statistically significant differences in the durations of response or survival times between the groups. The main side effects of CAP were: nausea and/or vomiting, leukopenia, anemia, thrombocytopenia, and renal toxicity. Leukopenia and anemia were the major toxic effects of *m*-AMSA. Our study supports the justification for testing phase II agent(s) in previously untreated patients with bladder cancer with systemic chemotherapy, provided adequate crossover to a known active single or combination of agents is built into the design of such a trial. [Cancer Treat Rep 69:189–194, 1985]

Systemic chemotherapy has usually been used in the treatment of locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium not amenable to surgical resection and/or radiotherapy. Many single agents, including cisplatin, have been found to be active against transitional cell tumors (1,3,4,6–11,15–23,31–33,36).

Combinations of chemotherapeutic drugs in TCC have yielded varying response rates (1,2,5,12–14,23, 30,36,37,39,40,43–46,49,52,53), but have not clearly demonstrated superiority over single agents in nonrandomized trials. Initial trials with the three-drug combination of cyclophosphamide, doxorubicin, and cisplatin (CAP) (46) suggested significant activity, with an overall response rate of 90%. Further studies with the same combination of agents did not confirm this high response rate (2,37,43,50).

Many single agents reported to be effective against bladder cancer as first-line therapy are less effective when given as a second or third agent (36,52). This is especially true for new phase II agents tested in patients with TCC of the bladder previously treated with systemic chemotherapy (34,35,51).

The drug amsacrine (*m*-AMSA) is one of many acridine derivatives which have antitumor activity in animals (54) and some human tumors (55).

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[3]Wayne State University Medical Center, Detroit, MI.

[4]Southwest Oncology Group Biostatistical Center, Houston, TX.

[5]University of Utah Medical Center, Salt Lake City.

[6]Henry Ford Hospital, Detroit, MI.

[7]University of Texas at Galveston.

[8]University of Kansas Medical Center, Kansas City.

[9]Scott and White Clinic, Temple, TX.

[10]University of Mississippi Medical Center, Jackson.

[*]*Reprint requests to:* Southwest Oncology Group (SWOG 7922), Operations Office, 4450 Medical Dr, San Antonio, TX 78229.

(SWOG) study comparing CAP versus *m*-AMSA, with crossover to the alternative treatment arm after failure or progression.

MATERIALS AND METHODS

Patients with histologically confirmed stage IV TCC of the urinary bladder or patients who had failed previous surgery and/or radiotherapy were entered in the study. All patients had measurable and evaluable lesions, with no prior systemic chemotherapy. Patients were informed of the possible toxic effects and experimental nature of this study and a written consent (in accordance with institutional and Food and Drug Administration guidelines) was obtained. Pretreatment evaluation consisted of a history and physical examination, multiphasic blood chemistry studies, cbc, platelet count, creatinine clearance determination, ECG, excretory urogram, and appropriate roentgenograms and scans. A BUN $\leq$ 20 mg/100 ml, serum creatinine $\leq$ 1.5 mg/100 ml and/or a creatinine clearance $\geq$ 60 ml/minute, bilirubin $\leq$ 1.5 mg/100 ml, wbc count $\geq 4000/mm^3$, and platelet count $\geq 100{,}000/mm^3$ were required.

Patients were separated into "good-risk" and "poor-risk" groups, the latter being defined as those $\geq$ 65 years of age with extensive prior radiation therapy or those with poor bone marrow reserve. Patients were randomized to receive either CAP or *m*-AMSA, with stratification according to good or poor risk.

CAP therapy was administered as follows. On Day 1, a minimum of 2 L of 5% dextrose in ½ normal saline was given iv. Cyclophosphamide at a dose of 600 mg/m^2 (500 mg/m^2 for poor-risk patients) by iv bolus and doxorubicin at a dose of 50 mg/m^2 (40 mg/m^2 for poor-risk patients) by iv bolus were given. Allopurinol at a dose of 300 mg orally daily was started and continued for the duration of the study. On the second day of the cycle, patients were given mannitol at a dose of 12.5 g by iv bolus before cisplatin at a dose of 75 mg/m^2 iv, followed by mannitol at a dose of 25 g in 1000 ml of 5% dextrose in water with 20 mEq of KCl over 4 hours iv. An additional minimum of 2 L of 5% dextrose in ½ normal saline was given over the next 24 hours. Additional fluids were administered to replace emesis losses. Courses were administered at 3-4-week intervals as hematologic and renal side effects returned to normal limits.

Those patients randomized to receive *m*-AMSA therapy were given 120 mg/m^2 (100 mg/m^2 for poor-risk patients) by iv infusion over 30-60 minutes in 250 ml of 5% dextrose in water. Courses were given every 3 weeks provided the hematologic side effects returned to normal limits.

Doses of doxorubicin, cyclophosphamide, or *m*-AMSA were adjusted in relation to the nadir blood cell counts encountered in the previous course of treatment. Doses of cisplatin were adjusted according to serum BUN, creatinine, and/or creatinine clearance after each cisplatin administration. No chemotherapy was given until all blood cell counts and renal function studies returned to normal.

Crossover from one treatment arm to the other was implemented in the event of disease progression after one course of therapy or stable disease after two courses.

A complete response (CR) was defined as the disappearance of all clinically detectable tumor. A partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of all diameters of measured lesions or, for patients with liver metastases, a 30% reduction in the sum of the measurements below the costal margin. No simultaneous increase in the size of any lesion or the appearance of new lesions had occurred. Stable disease was defined as steady-state or response less than PR or increasing disease less than progression. Disease progression was defined as an unequivocal increase of at least 50% in the size of any measurable lesion, the appearance of new lesion(s), uncontrolled hypercalcemia, or clearly progressive skeletal involvement manifested by increasing pain and the number of lytic lesions. Relapse was defined as the appearance of new lesion(s), the reappearance of old lesion(s) in patients who had CR, or an increase of $\geq$ 50% in the sum of the products of the diameters at the time of maximum response for patients achieving PR.

RESULTS

Forty-five patients who had not previously received systemic chemotherapy were entered in the study. Twenty-three patients initially were randomized to receive CAP and 22 were randomized to receive *m*-AMSA. Patient characteristics are shown in table 1 and the incidence of measurable lesions are shown in table 2. All patients were evaluated for response and drug toxicity. The responses to initial CAP therapy were: three patients with CR (13%); seven with PR (30%); six with stable disease (26%); and seven with disease progression (30%). The responses to initial *m*-AMSA were: one patient with CR (5%); three with PR (14%); six with stable disease (27%); and 12 with disease progression (55%). The differ-

TABLE 1.—Patient characteristics*

Characteristic	CAP	*m*-AMSA
Sex		
Male	16	16
Female	7	6
Age (yrs)		
Median	61	64
Mean	62	63
Range	44-75	46-77
Previous therapy		
Surgery	13	17
Radiotherapy	13	9

* Unless otherwise specified, values = No. of patients.

TABLE 2.—Sites of measurable disease*

Site	CAP (23 patients)	*m*-AMSA (22 patients)	Total (%)
Bone	10	9	19 (42)
Lung	7	9	16 (36)
Nodes	7	4	11 (24)
Pelvis	6	4	10 (22)
Liver	5	3	8 (18)
Bone marrow	0	1	1 (2)
Brain	0	1	1 (2)

* Values = No. of patients.

ence between the response rates of CAP (43%) versus *m*-AMSA (19%) was not statistically significant ($P = 0.067$) (by chi-square test unadjusted for continuity; $P = 0.11$, Fisher-Erwin test). Thirteen patients were crossed over to the CAP arm and were eligible to receive further chemotherapy after failing on initial *m*-AMSA treatment, while only three patients were crossed over to *m*-AMSA therapy. The responses to CAP after crossover were: two patients with CR, three with PR, four with stable disease, and four with disease progression. No patients on the *m*-AMSA crossover arm responded. The duration of response to second-line therapy was usually short. The overall responses to CAP (15 of 36 patients; 42%) and to *m*-AMSA (four of 25; 16%) are shown in table 3.

The overall toxic effects resulting from chemotherapy are shown in table 4. Nausea and/or vomiting, leukopenia, anemia, thrombocytopenia, and renal toxicity were the main side effects of CAP. Leukopenia and anemia were the major toxic effects of *m*-AMSA. One patient experienced arrhythmia while receiving *m*-AMSA. The degree and severity of the toxic effects of CAP as first-line therapy are shown in table 5 and of m-AMSA as first-line therapy in table 6. One patient died from life-threatening leukopenia due to CAP treatment. Two patients had severe but reversible renal toxicity from CAP therapy (serum creatinine of 4.0 mg/100 ml and/or creatinine clearance of ⩽ 40 ml/minute). The median duration of response to CAP was 28 weeks (range, 6–65+), while the median duration of response to *m*-AMSA was 21 weeks (range, 6–36). There was no statistically significant survival difference between patients treated initially with CAP versus *m*-AMSA (two-tailed *P* values; 95% confidence; Breslow/Gehan, 0.38; long-rank, 0.64) as shown in figure 1. The overall survival curve for all patients (45) treated in this study is shown in figure 2.

TABLE 3.—Overall response rate to chemotherapy*

Response	CAP	*m*-AMSA
CR	5 (14)	1 (4)
PR	10 (28)	3 (12)
Stable disease	10 (28)	8 (32)
Progressive disease	11 (30)	13 (52)
CR + PR/total	15/36 (42)	4/25 (16)

* Values = No. of patients (%).

DISCUSSION

Many single agents and combinations of chemotherapeutic drugs have been tested in the palliative treatment of patients with advanced and recurrent TCC of the urothelium. The reported response rates to single- or combination-agent chemotherapy vary from one institution to another. This may be as a result of patient selection and characteristics, performance status, previous radiation therapy to recurrent measurable lesion(s), and previous exposure to systemic chemotherapy. Also, the response rate reported is usually higher if only evaluable patients were selected versus all patients entered.

Three single agents (doxorubicin, methotrexate, and cisplatin) have been tested extensively in the treatment of patients with advanced and metastatic cancer of the urinary bladder. Most of the responses were PRs and usually of very short duration. Various dose schedules had been used in these trials. The reported response rate to doxorubicin varies from 10% to 40% (4,6,15,22,23,36); the response rate to methotrexate ranges from 9% to 36% (16,20); and the response rate to cisplatin ranges from 26% to 57% (36,38,41,42,47,48,50). It does seem clear from these nonrandomized studies that cisplatin therapy may be the most effective single agent in the treatment of patients with advanced bladder cancer. Trials of single agents in patients with bilharzial bladder cancer failed to show antitumor activity to bleomycin (7), methotrexate (8), etoposide (9), doxorubicin (10), or cisplatin (11). The only active drug in these patients was hexamethylmelamine (9).

In an effort to improve the results obtained with single agents in the palliative management of patients with ad-

TABLE 4.—Incidence of overall toxicity*

Toxic effect	CAP (36 patients)	*m*-AMSA (25 patients)
Nausea/vomiting	22 (61)	3 (12)
Leukopenia	25 (69)	12 (48)
Anemia	21 (58)	5 (20)
Thrombocytopenia	9 (25)	1 (4)
Renal	8 (22)	—
Diarrhea	1 (3)	—
Mucositis	1 (3)	—
Cardiac	1 (3)	1 (4)

* Values = No. of patients (%).

TABLE 5.—Degree of toxicity to CAP as first-line therapy*

Toxic effect	Degree					
	None	Mild	Moderate	Severe	Life-threatening	Fatal
Nausea/vomiting	8	3	7	4	1	—
Leukopenia	5	—	8	5	4	1
Anemia	8	6	4	5	—	—
Thrombocytopenia	16	3	—	2	2	—
Renal toxicity	17	2	2	2	—	—

* Values = No. of patients.

vanced TCC of the urothelium, many noncisplatin combinations (5,12-14,23-30,36) and cisplatin combination regimens (1,2,37,39,40,43-46,49,50) have been investigated. The most common noncisplatin combination has been 5-FU and doxorubicin (5,12-14). In each of four reports, the overall response rate was about 35% (range, 31%-40%).

With the introduction of cisplatin as an active agent against malignant tumors of the urothelium, many cisplatin combinations have been investigated in these patients. The most common cisplatin combinations were cisplatin and cyclophosphamide (1,36,44,45,50), cisplatin and doxorubicin (49,50), and CAP (2,37,43,46,50). Early reports with preliminary results suggested a very high response rate with CAP in patients with advanced cancer of the urothelium (46). This led to the trial of the same three drugs, with some modification of doses because of the unacceptable toxic effects in patients with advanced TCC of the urinary bladder (2,37,43,50). The response rates to CAP in subsequent trials were: 50% (50), 33% (43), and 38% (37). In our SWOG study the overall response rate to the same CAP combination was 42%. Yagoda (50), in a nonrandomized trial, reported that the response rates of cisplatin alone, cisplatin and cyclophosphamide, cisplatin and doxorubicin, and CAP in patients with advanced bladder cancers were 36%, 43%, 54%, and 50%, respectively. Schwartz et al (2) reported recently that responders to CAP therapy live significantly longer than nonresponders.

The response rates of investigational agents in patients with urothelial cancers, especially those previously treated with systemic chemotherapy, have been poor (34,35,51). Very few randomized studies utilizing systemic chemotherapy in this disease have been reported. One such study from SWOG was reported by Gagliano et al (49) in 1983 comparing doxorubicin versus doxorubicin and cisplatin. The response rates were 19% and 43%, respectively ($P = 0.02$). No statistical difference was found in the median duration of response or in survival between the two groups, while responders had significantly better survival than nonresponders ($P = 0.02$).

The main purpose of the current study was to confirm the results of CAP therapy on a group-wide level and to study a promising phase II drug (*m*-AMSA) in previously untreated patients with systemic chemotherapy. The study was designed as a phase II trial, with a crossover mechanism to test the effect of the initial therapy when given as second-line treatment. In 22 patients treated, the response rate to initial *m*-AMSA was 19%, with one CR and three PRs. Recently, and since the initiation of our study, Natale et al (51) reported on the activity of *m*-AMSA in previously treated patients with bladder cancer. Two of 21 evaluable patients (9.5%) experienced PR (22 were entered). While Trump et al (56) reported a response in 15 patients treated with *m*-AMSA, all had previously failed at least one systemic chemotherapy regimen. In our trial, a small number of patients (three) were crossed over after failure on CAP therapy to the *m*-AMSA arm. None experienced a response to this phase II second-line treatment. Of those patients who failed *m*-AMSA but were then treated with CAP, five of 13 (two CRs; three PRs) responded. The difference in initial response rates between the two groups of patients was not statistically significant. No statistical difference was found in the duration of response or in the overall survival to initial therapy with CAP versus *m*-AMSA. This study was designed as a phase II trial to test CAP response rate on the group level and to investigate the response to a phase II agent in patients previously untreated with chemotherapy. Due to the small number included, one should be cautious in reaching a definite conclusion, because there is no difference in overall survival

TABLE 6.—Degree of toxicity to *m*-AMSA as first-line therapy*

Toxic effect	Degree				
	None	Mild	Moderate	Severe	Life-threatening
Leukopenia	12	4	4	1	1
Anemia	18	1	2	1	—
Thrombocytopenia	21	—	1	—	—
Nausea/vomiting	19	1	1	1	—

* Values = No. of patients.

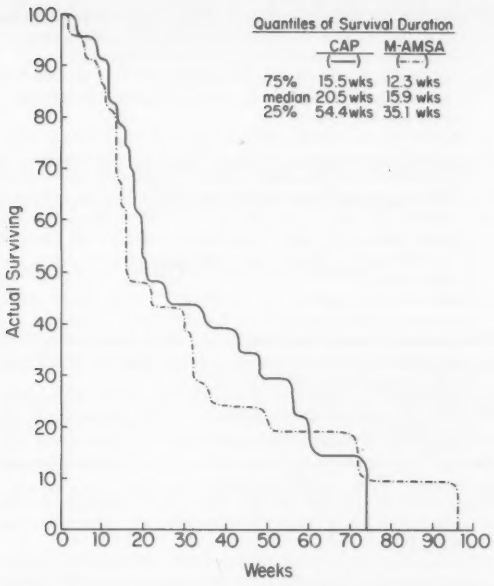

FIGURE 1.—Overall survival in wks of patients who received initial CAP vs *m*-AMSA (by Kaplan and Meier).

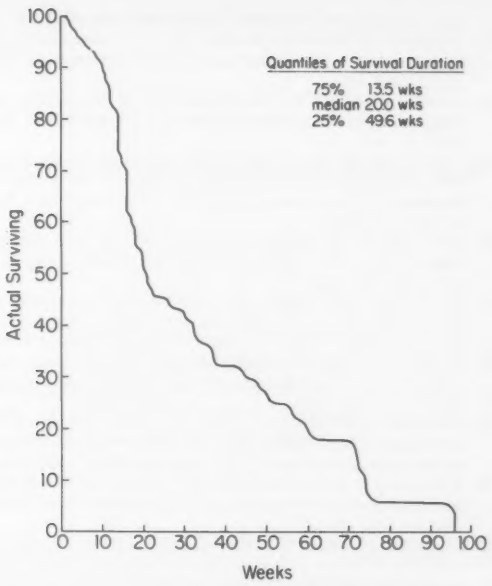

FIGURE 2.—Overall survival of patients with TCC of the bladder treated with chemotherapy (by Kaplan and Meier).

between the two treatment arms. This is an important finding and supports the justification of investigating promising phase II agent(s) up front, provided adequate crossover to a known single active or combination of agents is built into the design of the trial.

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Double Labeling of Human Leukemic Cells Using ^{3}H-Cytarabine and Monoclonal Antibody Against Bromodeoxyuridine[1,2]

Azra Raza* and Harvey D. Preisler[3,4]

A new technique using immunofluorescence and autoradiography is described, in which the DNA of cells in S phase are labeled with two different probes. This method makes it possible to study the relationship between DNA synthesis and the uptake and/or incorporation of chemotherapeutic agents into normal or neoplastic cells. An example is provided in which the incorporation of ^{3}H-cytarabine into DNA is demonstrated to occur only in cells which were synthesizing DNA during exposure to ^{3}H-cytarabine. Other radioactively labeled probes can be used as well. [Cancer Treat Rep 69:195–198, 1985]

Autoradiographic recognition of tritiated thymidine (^{3}HTdR) incorporation into the DNA of cells provides an accurate assessment of percent S-phase cells in a population. Double labeling studies utilizing two different isotopes such as ^{3}H- and ^{14}C-TdR are tedious to perform and often produce inconsistent results, since the only way to distinguish between the ^{3}H and ^{14}C label is based on the energy differences of the electrons emitted by the two isotopes (1).

We have produced a monoclonal antibody (RPMB I) against bromodeoxyuridine (BrdU) which can easily detect BrdU that has been incorporated into DNA, thereby providing a precise measurement of the percentage of cells which are in S phase (2). By combining this immunofluorescent method with conventional autoradiographic techniques we directly demonstrated that all cells which incorporated BrdU into their DNA also incorporated ^{3}HTdR, thus validating the fluorescent method for estimating the percentage of cells in S phase. This observation raised the possibility of a new "double label" method for studying the relationship between the incorporation of cytarabine (araC) into DNA and the S-phase status of human leukemic cells.

The studies reported here demonstrate that araC is incorporated into DNA only in those cells which were synthesizing DNA during incubation with araC. Additionally, this method has the potential for recognizing cells in S phase which do not incorporate araC into DNA and hence are metabolically resistant and for quantitating the relationship between araC incorporation into DNA and the effects of the drug on DNA synthesis.

MATERIALS AND METHODS

Bone marrow (BM) samples were obtained from five patients with acute or chronic myeloid leukemia. Rbcs were removed by centrifugation on Ficoll Hypaque. The interphase cells were gently removed and washed three times in RPMI-1640 medium. Cells at a concentration of 1×10^7 cells/ml were incubated for 2 hours at 37°C in 5% CO_2 in the following groups.

(*a*) ^{3}HTdR (10 μCi/ml; specific activity, 77 Ci/mmol) together with 10^{-5} M floxuridine (Fudr). Cells were washed once in cold TdR and thrice in phosphate-buffered saline (PBS) and processed for autoradiography as described below.

(*b*) 10^{-4} M BrdU and 10^{-5} M Fudr and processed by RPMB technique described below.

(*c*) ^{3}HaraC (10 μl of 1 mCi/ml of ^{3}HaraC; specific activity, 15.5 Ci/mmol) and processed for autoradiography as Group 1.

(*d*) ^{3}HTdR (10 μl), BrdU (10^{-4} M), and Fudr (10^{-5} M) and processed for double labeling described below.

(*e*) ^{3}HaraC (10 μl), BrdU (10^{-4} M), and Fudr (10^{-5} M) and processed for double labeling.

RPMB I Antibody

This is a monoclonal antibody prepared by standard

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[3]Leukemia Service, Roswell Park Memorial Institute, Buffalo, NY.

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* *Reprint requests to:* Azra Raza, MD, Leukemia Service, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

TABLE 1.—Human leukemic cells from 5 patients studied for single and double labeling by using ^{3}HTdR, BrdU, and ^{3}HaraC

Patient No.	Single labeling (%)			Double labeling (%)	
	^{3}HTdR	BrdU	^{3}HaraC	BrdU/^{3}HTdR	BrdU/^{3}HaraC
1	14	18	16	11/8	14/6
2	18	14	18	13/13	11/9
3	6	6	6	7/7	7/7
4	10	9	7	9/9	9/7
5	5	3	2	6/6	3/2

cell fusion procedures for producing hybridomas using spleen cells from mice immunized with bromouridine and x-63/Ag-8.653 HAP-sensitive myeloma cells. The monoclonal antibody has been shown to be highly specific for BrdU (manuscript in preparation). Concentrations of TdR as high as 10^{-3} M did not inhibit binding in a radioimmunoassay, while BrdU at 10^{-5} M effectively competed with the antigen in a radioimmunoassay.

RPMB Technique

Groups 2, 4, and 5 were processed as follows. After completing incubations, cells were resuspended in PBS. Three drops of this suspension were pipetted onto Alcian Blue-coated coverslips and fixed in 70% ethanol for 10 minutes. After washing, the coverslips were covered with 4 N HCl for 20 minutes at room temperature (RT). Cells were then exposed to Tris buffer containing 0.1% bovine serum albumin (BSA) for 1 hour at 37°C in 5% CO_2. RPMB I diluted 1:100 with PBS/0.05% NP40 was pipetted on each coverslip for 1 hour at RT. Coverslips were rinsed in PBS/Triton X-100 (0.1%) for 30 minutes and exposed to FITC-conjugated goat antimouse antibody (Tago) diluted 1:20 with PBS/1% goat serum for 30 minutes at RT. A final rinse for 30 minutes was carried out in PBS/Triton X-100 followed by rinsing with distilled wa-

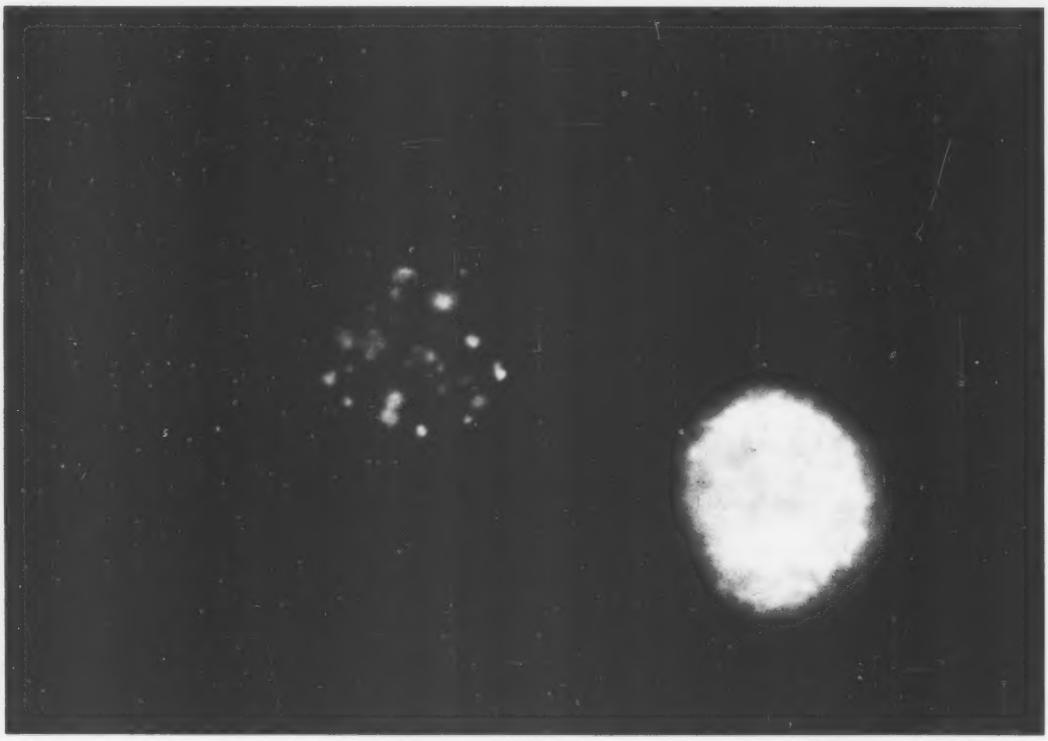

FIGURE 1.—BM cells of a patient with acute nonlymphocytic leukemia processed by the RPMB technique. Two S-phase cells show bright fluorescence along with 2 clearly nonfluorescent cells. Note the distinctly different patterns of fluorescence in the positive cells.

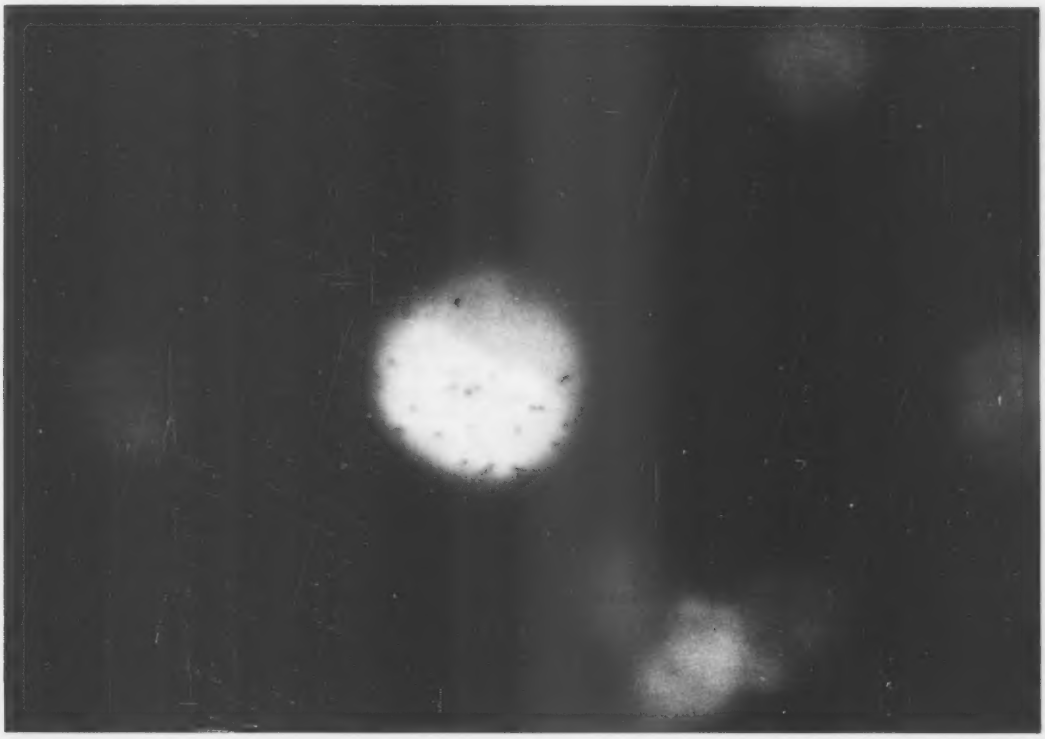

FIGURE 2.—BM cells from a patient with acute nonlymphocytic leukemia incubated with BrdU and ^{3}HTdR simultaneously. After processing with RPMB technique and autoradiography, double labeling of an S-phase cell is clearly seen. Negative cells show neither fluorescence nor black grains.

ter. The coverslips were then ready to be examined in a fluorescence microscope.

Autoradiography

Slides from Groups 1 and 3 and RPMB-processed coverslips from Groups 4 and 5 were coated with NTB2 nuclear track emulsion (Eastman Kodak) and exposed in the dark for 24 hours. Groups 3 and 5 were exposed for 1 week. All exposures in the dark were at -80°C. D-19 developer was used to develop the samples and after fixing, slides were stained with May-Grünwald-Giemsa stain and coverslips were mounted on glass slides with Elvanol and examined under a fluorescence microscope. Results were read by a single observer counting at least 300 cells from two to four slides.

RESULTS

Figure 1 illustrates the appearance of cells which were or were not in S phase during incubation with BrdU. Two cells are positive and two are negative. Note that the amount and pattern of fluorescence in the positive cells are quite different, indicating a difference in incorporation of BrdU by each cell, most probably due to differences in the duration of BrdU incorporation into DNA. Figure 2 illustrates the labeling pattern of a cell which was simultaneously incubated with BrdU and ^{3}HTdR. Note that only the fluorescent cell has grains over its nucleus.

Table 1 describes double label studies performed on BM samples obtained from five patients. When ^{3}HTdR and BrdU were used simultaneously, virtually every cell in S was simultaneously fluorescent and produced grains in the overlying emulsion. When BrdU and ^{3}HaraC were used together, most S-phase cells demonstrated both ^{3}HaraC grains and fluorescence. There were a few cells, however, in every patient except one (Patient 3), that showed only fluorescence and no ^{3}HaraC incorporation. The number of grains of ^{3}HaraC and the degree of fluorescence varied from cell to cell in the same patient as well as from patient to patient.

DISCUSSION

The double label method described here is simple to

perform, takes a short period of time to carry out, and even unskilled individuals can distinguish between cells which are singly or doubly labeled. This method is directly applicable to cell cycle studies which require double labeling of DNA (3) as well as to studies of the uptake and incorporation of chemotherapeutic agents by cells and the effects of such on DNA synthesis. As demonstrated here, only cells synthesizing DNA during incubation with ^{3}HaraC incorporated araC into DNA. Presumably, S-phase cells which fail to do so would be resistant to araC. A prospective clinical study of this proposition is under way.

In our initial and ongoing studies we have noted that the degree of cellular fluorescence and the number of ^{3}HaraC grains overlying the nucleus appear to be inversely related in araC-sensitive cell populations. Automated quantitation of total cellular fluorescence together with grain counting may permit a precise determination of araC sensitivity of a cell population as a whole as well as the recognition and quantitation of the number of araC-sensitive or -resistant cells which are present. The ability to do so would permit rational approaches to chemotherapy.

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Hypersensitivity Reactions to Amsacrine[1,2]

David J. Perry,[3,*] Raymond B. Weiss,[3] and Daniel F. Hoth[4,5]

Five cases of hypersensitivity reactions to amsacrine are reported. These five cases are compared to the three cases previously published. Sixty-two reports on the clinical use of amsacrine in a variety of solid tumors and hematological malignancy were reviewed. Nine cases of hypersensitivity were described in the 2095 patients reported in these clinical trials. The approximate incidence of hypersensitivity to amsacrine is 0.4% [Cancer Treat Rep 69:199–201, 1985]

Many cancer chemotherapeutic agents can cause hypersensitivity reactions, and the subject has been recently reviewed in detail (1,2). Most of these reactions are type I and are characterized by urticaria, bronchospasm, angioedema, and occasionally hypotension. Amsacrine, an acridine derivative useful in the treatment of acute leukemia, has been reported to cause type I reactions in three cases (3–5). We describe five additional cases reported to the Investigational Drug Branch of the National Cancer Institute.

The five cases were reported to the Investigational Drug Branch from June 1980 to December 1981. Sixty-two published reports on the clinical use of amsacrine in a variety of solid tumors and hematological malignancy were also surveyed for mention of hypersensitivity reactions. Three published cases of amsacrine hypersensitivity were reviewed. The clinical data were analyzed and abstracted.

CASE REPORTS

Patient 1

A 61-year-old woman with stage I chronic lymphocytic leukemia and malignant melanoma had received a year of treatment with dacarbazine and dactinomycin, with prochlorperazine im as premedication. Her disease progressed and she began treatment with amsacrine. Twenty minutes prior to the first dose of amsacrine she received im prochlorperazine. The patient had received about 40% of her 120-mg/m^2 dose of amsacrine when she complained of lightheadedness. She was noted to have an irregular pulse at a rate of 36. The amsacrine was stopped, and shortly after she suffered a grand mal seizure and became apneic and pulseless. Cardiopulmonary resuscitation was started, but the patient began labored breathing after a few chest compressions and Ambu bagging. She was noted to have a large wheal extending up her left arm. She was treated with iv diphenhydramine and improved; she subsequently recovered completely. The attending physician believed that the patient suffered an anaphylactoid reaction with secondary cardiac problems.

Patient 2

A 49-year-old man who had failed prior induction therapy with doxorubicin and cytarabine for promyelocytic leukemia was placed on an etoposide and amsacrine protocol. While the amsacrine was infusing via Hickman catheter, the patient developed a pruritic macular rash over the arms and trunk. There was concomitant hypotension but no bronchospasm. The patient was given diphenhydramine and the infusion was continued. The patient was later rechallenged with amsacrine; a rash and a blood pressure drop from

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[2]The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

[3]Hematology-Oncology Service, Walter Reed Army Medical Center, Washington, DC, and Uniformed Services University of the Health Sciences, Bethesda, MD.

[4]Investigational Drug Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

[5]We acknowledge the following investigators who contributed clinical information: Scott Boswell, Yuang-Chi Chang, M. Harris, Frank L. Meyskens, Jr, Frank J. Panettiere, Tom Simpson, and Douglass C. Tormey.

* *Reprint requests to:* David J. Perry, MD, MAJ, MC, Hematology-Oncology Service, Department of the Army, Walter Reed Army Medical Center, Washington, DC 20307.

120/80 to 90/60 were noted. Amsacrine was discontinued.

Patient 3

A 14-year-old boy with Ewing's sarcoma received amsacrine infusion. Ninety minutes into the infusion, urticaria developed over the chest and face, without pruritus. There was no hypotension. The infusion was continued and the urticaria disappeared over 10–15 minutes. Ninety minutes after the infusion, the patient developed fever to 103.4°F.

Patient 4

A 29-year-old woman received amsacrine for acute leukemia. Within 15 minutes of her third daily dose of 100 mg of the drug, she developed a macular rash involving the trunk, arms, and face, but sparing the legs. This rash resolved after 50 mg of iv diphenhydramine. The next day, the patient was premedicated with 50 mg of diphenhydramine and 100 mg of hydrocortisone, and a small test dose of amsacrine was given. No reaction was seen and full doses of 100 mg were given on the fourth and fifth days after premedication with diphenhydramine and hydrocortisone. No further rash was noted.

Patient 5

A 71-year-old man with squamous carcinoma of the lung had received irradiation and chemotherapy with cyclophosphamide, doxorubicin, methotrexate, and procarbazine. He began treatment with amsacrine (250 mg in 500 ml of 5% dextrose in water) by slow infusion over 1–2 hours on Days 1 and 29. On Day 57, he received the same dose by the same administration method. He developed erythematous papules along the injecting vein about 5 minutes after the infusion was started. The left forearm became diffusely erythematous and swollen after 30 minutes. The patient complained of modest itching over the left forearm; there was no itching over other parts of the body and no wheezing, dyspnea, or hypotension. The infusion was stopped after 1 hour and the patient was treated with local ice packs over the left forearm and iv diphenhydramine. The erythema and edema subsided within 48 hours. The attending physicians believed that this reaction was more than a simple phlebitis and instead represented a local hypersensitivity reaction.

LITERATURE REVIEW

To estimate the incidence of allergic reactions to amsacrine, 62 trials published between 1980 and 1983 were reviewed. These trials reported on 2095 patients treated for a variety of solid tumors, leukemias, and lymphomas. Nine cases of hypersensitivity were described (7–12). Five patients had urticaria: three had an acute erythematous skin reaction with itching; and one had anaphylaxis. The approximate incidence of such reactions to amsacrine is 9/2095 or 0.4%.

There have been three previous reports of amsacrine hypersensitivity (3–5): two patients developed an acute erythematous nonurticarial rash and one pharmacy worker developed urticaria on three separate occasions after mixing the drug. In addition, nine nurses or pharmacy personnel developed symptoms of nausea, lightheadedness, and malaise within hours of mixing amsacrine.

Treatment for the urticaria or erythematous eruption was iv diphenhydramine or corticosteroids. In two cases in which it was tried, hydrocortisone prevented rash on rechallenge with amsacrine.

DISCUSSION

We have described five patients who developed hypersensitivity reactions to amsacrine and have reviewed the descriptions of 12 other cases of such toxicity. Although amsacrine is a known cause of seizures, the combination of local wheal, seizure, and cardiac arrest in Patient 1 is more consistent with an anaphylactoid reaction. Although the incidence of these reactions is low, when they occur they can be life-threatening, as seen in our Patient 1.

The clinical features of amsacrine hypersensitivity have been those characteristic of type I reactions, such as rash, urticaria, and hypotension. One atypical feature was acute "phlebitis." This may actually be a localized angioedema and thus a localized hypersensitivity reaction analogous to that sometimes noted from doxorubicin (1,2).

It appears that amsacrine can be given again to patients whose only reaction is a rash. In two of the cases in this series, re-treatment with amsacrine produced no reactions or just another mild rash. Inadequate data exist to estimate the risk of rechallenge in patients who developed hypotension or other signs of anaphylaxis. The one patient in our series who was rechallenged developed hypotension a second time.

The mechanism of these reactions has not been investigated. Some cancer chemotherapeutic drugs seem to stimulate mast cells and basophils to release vasoactive substances by nonimmunologic means (1,2). Since three of the patients analyzed here had reactions from their first exposure to amsacrine, it is unlikely that these reactions were mediated immunologically.

Although an uncommon problem, health care personnel administering amsacrine should be aware that hypersensitivity reactions do occur with infusion of the

drug. Patients should be monitored in a setting that allows quick access to resuscitative drugs and equipment.

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Vindesine-Prednisone in the Treatment of Blast Crisis of Chronic Myeloid Leukemia[1]

F. Lemoine, A. Najman,* J. P. Laporte, N. C. Gorin, and G. Duhamel[2]

Eight patients with chronic myeloid leukemia in blast crisis were treated with a combination of vindesine and prednisone. Complete remission was achieved in three patients; partial remission was achieved in three. All six responders received maintenance treatment with hydroxyurea and 6-mercaptopurine. The median duration of survival was 9 months. Two patients had long-term survival: one survived 32 months and the other is alive after 30 months. These data suggest that vindesine-prednisone polychemotherapy might improve the prognosis of blast crisis in chronic myeloid leukemia. [Cancer Treat Rep 69:203–204, 1985]

Blast crisis, as the obvious cause of death in chronic myeloid leukemia (CML), has been reported to occur in 60%–90% of patients with CML. The usual pattern is a myeloid blast crisis with an increasing number of promyelocytes and myeloblasts. A great spectrum of morphologic variety could, however, be observed: erythroblastic, megakaryoblastic (1), and undifferentiated transformation. Lymphoid blast crisis could also occur.

Until recent years, the different chemotherapeutic regimens employed in the treatment of CML in blast crisis remained disappointing. The median survival was < 7 months (2).

In 1978, Mathé et al (3) reported better results in patients treated with vindesine (VDS). Our study reports the first results obtained with the combination of VDS and prednisone in induction, and hydroxyurea (HU) and 6-mercaptopurine (6-MP) in maintenance for the treatment of eight adult patients with blast crisis of chronic myelogenous leukemia (BCML).

PATIENTS AND METHODS

Eight consecutive patients with BCML were treated with our therapeutic protocol. There were five males and three females ranging in age from 26 to 57 years.

The diagnosis of blast crisis was based on the following criteria (4): (*a*) the presence of > 50% of myeloblasts and promyelocytes in the bone marrow and/or > 30% of the same cells in the peripheral blood; and (*b*) blast infiltration in the bone marrow biopsy specimen. Anemia, thrombocytopenia, and an increase of basophils were also indicative.

Hematologic studies were performed by May-Grünwald Giemsa staining of smeared bone marrow aspirates and peripheral blood. Cytochemical analysis was done using peroxidase and periodic acid-Schiff staining. The cellular types were myeloblastic (five cases), lymphoid (one), and undifferentiated (two). Cytogenetic analysis performed on the bone marrow cells revealed the following: persistence of Ph 1 only, already observed during the chronic phase (five cases); duplication of Ph 1 (one); and hyperploidy with a double Ph 1 (one). The analysis failed in one case.

Treatment Schedules

Prior to our protocol, none of the patients had been treated with vinca alkaloids.

Induction.—VDS was given by iv injection at a dose of 2 mg/m^2/day during 2 consecutive days (one cycle) once weekly. The number of cycles (two to four) and the total dose given were determined by the results obtained. Simultaneously, daily doses of 1 mg/kg of prednisone were given orally during the induction regimen.

Maintenance.—Daily doses of HU and 6-MP were given orally. The doses were adjusted according to peripheral leukocyte and platelet counts. Every month, one cycle of VDS was given iv at a dose of 2 mg/m^2/day during 2 days.

Whenever required, the patients received supportive therapy with broad-spectrum antibiotics, platelets, and packed rbc transfusions.

[1]Received Feb 3, 1984; revised July 30, 1984; accepted Aug 9, 1984.
[2]Service des Maladies du Sang, Hôpital Saint-Antoine, Paris, France.
*Reprint requests to: A. Najman, Service des Maladies du Sang, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75012-Paris, France.

Response to Therapy

The efficacy in terms of complete remission (CR), partial remission (PR), or failure, and the toxic effects were recorded. A CR is defined as the disappearance of all perceptible manifestations, clinical manifestations, and blood and bone marrow blast cells for a minimum of 4 weeks. A PR is defined as the reduction of marrow blasts to < 30%. Only the responding patients (CR + PR) received the maintenance treatment.

RESULTS

Efficacy

A significant decrease in peripheral blast cell count was observed in all patients but two. Five patients had splenomegaly: the spleen volume decreased to normal (one patient), partially decreased (three), or was not affected by therapy (one). After induction treatment, three patients were in CR: two with four cycles and one with three cycles. Three patients were in PR: one with four cycles, one with three cycles, and one with two cycles. Two failures occurred despite four and two cycles of treatment, respectively. The six patients in CR and PR received maintenance treatment.

Duration of survival varied from 5 to 32 months. Two patients with the myeloblastic pattern lived longer. The one patient who survived 32 months was in CR until the 16th month after four cycles of treatment; a relapse then occurred and a new series of three cycles was given which allowed a PR for another 16 months. The other patient in PR is relapse-free after 30 months. Six patients have died: five from septic shock and one from severe hemorrhagic complications. The median duration of survival from the onset of blast crisis was 9 months. The duration of the responses could not be predicted from our data because, as soon as a complete and/or partial remission was obtained, the patients were switched to reinduction or maintenance chemotherapy.

Tolerance

The main manifestation of toxicity was hematologic. The wbc count fell to < 2500/mm^3 in six patients, with a mean nadir of 1100/mm^3 on Day 19. All eight patients had thrombocytopenia prior to VDS administration; a decrease in platelet count to < 10×10^9/L was recorded in four cases. None of the nonhematologic side effects such as neurologic toxicity (constipation, paresthesia, hyporeflexia), vomiting, and general intolerance was severe.

DISCUSSION

The use of VDS in BCML has allowed us to obtain a CR and/or PR in 75% of the cases (six of eight patients). Therapy response allowed a total median survival of 9 months.

The different therapeutic protocols used before VDS were not as successful. In a retrospective study involving 50 patients treated with different chemotherapies, Mandelli et al (2) reported only 38% of responders. In a partially randomized study with 202 patients treated with HU, 6-MP, and corticosteroids, Coleman et al (5) observed only 34% of responders with a median survival of 12 weeks. From 1978, the use of VDS in BCML by several investigators (3,6,7) has improved these data considerably. Hence, Mathé et al (8) have achieved CR in ten of 24 patients.

After vinblastine and vincristine, VDS is a new vinca alkaloid. VDS is more toxic than vinblastine but less toxic than vincristine, and its most remarkable characteristic is the absence of cross-resistance with vincristine (3). VDS may be administered by different modes: (*a*) discontinuous administration at a dose of 4 mg/m^2/week in 2 days and (*b*) continuous infusion over 5 days. In this study, we used the first mode and we now intend to try the second mode, which might improve the efficacy of VDS (7).

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Intracavitary Cisplatin Chemotherapy for Mesothelioma[1,2,3,4]

Craig E. Pfeifle, Stephen B. Howell,* and Maurie Markman[5]

A feasibility study of intracavitary cisplatin was conducted in eight patients with mesothelioma. Cisplatin, 90 mg/m², was instilled weekly for 3 weeks, followed by a 3-week rest; thiosulfate was given iv to reduce nephrotoxicity. In 50 courses there was no chemical serositis; the major toxic effect was myelosuppression. One patient with measurable disease had a complete response; three others had objective responses. [Cancer Treat Rep 69:205–207, 1985]

Cisplatin can be safely administered into the pleural and peritoneal cavities, producing respective intracavitary drug concentrations that are 130–240-fold[6] and 20–30-fold greater than peak plasma concentrations (1). In this study we examined the feasibility of using intracavitary cisplatin in a weekly × 3 schedule in eight patients with mesothelioma. The choice of a weekly schedule was based on studies in ovarian carcinoma suggesting greater activity of cisplatin on a weekly schedule (2).

METHODS

Eight males, 33–73 years of age (median, 61), with malignant mesothelioma consented to participate. All patients except Patient 6 had a documented history of asbestos exposure. Entry criteria included serum creatinine < 1.5 mg/dl; blood urea nitrogen < 40 mg/dl; wbc count > 3000/mm³; platelet count > 100,000/mm³; and life expectancy > 1 month. The patient characteristics and presentations are shown in table 1. In all cases the pathologic material was examined with special stains (mucicarmine, alcian blue with or without prior treatment with hyaluronidase) and was reviewed by at least three pathologists in separate institutions.

Patients were hydrated with 1 L of 0.9% sodium chloride iv and 1 L orally over 1 hour prior to treatment. The cavity was drained as completely as possible and cisplatin, 90 mg/m² diluted in 0.25 (pleural) or 2.0 (peritoneal) L of 0.9% sodium chloride, was instilled over 15 minutes. After a 4-hour dwell, the cavity was again drained. Concurrent with the instillation of cisplatin, an iv bolus of furosemide (20 mg) and sodium thiosulfate (4 g/m²) were administered, and a 5-hour iv infusion of thiosulfate 10 (g/m²) was started. Each treatment cycle consisted of three weekly treatments followed by a 3-week rest. Cycles were repeated at 6-week intervals.

RESULTS

Toxicity

Eight patients received a total of 50 treatments (16⅔ cycles) of therapy on the weekly cisplatin protocol. Forty-five treatments were evaluable for nephrotoxicity. Serum creatinine rose by > 25% following therapy in only three courses. Likewise, posttreatment creatinine exceeded 1.2 mg/dl in only three courses and 1.5 mg/dl in only one course. There was no significant difference between pretreatment and posttreatment creatinine levels ($n = 45$, $P = 0.22$; two-tailed paired t test), or between initial on-study and off-study creatinine levels ($n = 8$, $P = 0.42$; two-tailed paired t test). Urinalysis obtained prior to each treatment were unchanged over the course of the study.

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[5]Department of Medicine, the Cancer Center and the General Clinical Research Center, University of California, San Diego.

[6]Howell SB. Unpublished data.

**Reprint requests to:* Stephen B. Howell, MD, University of California San Diego Cancer Center, T-012, La Jolla, CA 92093.

TABLE 1.—Patient characteristics, presentations, and responses

Patient No.	Age (yrs)	Cavity involved	Protocol	Courses	Histology	Prior therapy	Presentation	Response*	Survival (months)†
1	54	Pleural‡ and peritoneal	Weekly	7	Mixed	None	Severe pleural encasement, massive ascites, positive cytology	MR—resolution of ascites, no change in cytology or pleural disease	8
2	61	Pleural	Weekly	2	Epithelial	None	Pleural thickening, small pleural effusion	NR—no change	11
3	66	Pleural	Weekly	3	Epithelial	None	Pleural effusion and thickening	NE—patient died 5 wks after last therapy of pericardial constriction, no clinical improvement from therapy, autopsy showed various degrees of tumor necrosis in treated cavity	2
4	73	Peritoneal	Weekly	3	Subtype not defined	None	Massive ascites, peritoneal studding, positive cytology	NR—no change	5
5	65	Pleural	Weekly	9	Mixed	None	Large pleural effusion, pleural thickening	MR—decreased pleural effusion, decreased pleural thickening	7.5
6	33	Peritoneal	Weekly	6	Epithelial	None	Massive ascites, pleural effusion	NR—no change	4.5
7	62	Pleural‡ and peritoneal	Weekly	9	Subtype not defined	None	Massive ascites, peritoneal studding, pleural thickening	MR—resolution of ascites, treatment continuing	10+
8	57	Peritoneal	Weekly	11	Epithelial	Doxorubicin	Massive ascites, widespread peritoneal studding, positive cytology	CR—resolution of ascites, conversion of cytology, peritoneum free of gross and microscopic tumor at laparotomy	22+

* CR = complete response; MR = objective improvement; NR = no response; and NE = not evaluable.
†From first ip treatment.
‡Pleural cavity not treated.

Hematologic toxicity was moderate. Geometric mean pretreatment and nadir wbc counts were 6.8 × $10^3/mm^3$ (range, 3.3-13.2) and 4.9 × $10^3/mm^3$ (range, 2.8-9.8), respectively. Similarly, the geometric mean pretreatment and nadir platelet counts were 379 × $10^3/mm^3$ (range, 169-597) and 219 × $10^3/mm^3$ (range, 91-356), respectively. Nadir platelet counts fell to < 100,000 cells/mm^3 in only one cycle. The mean time to nadir for both indices was 14 days beyond the last treatment in each cycle. In patients receiving more than one treatment cycle, nadir counts did not vary significantly from cycle to cycle ($P > 0.05$, analysis of variance).

Intracavitary cisplatin did not produce symptoms or signs of chemical peritonitis or pleuritis. One patient developed bacterial peritonitis with *Staphylococcus epidermidis* 3 weeks after his last treatment, after gross contamination of his catheter. In two patients the serosal surfaces were examined directly at laparotomy or autopsy within 4 weeks of the last treatment. In neither of these patients were there any macroscopic or microscopic changes in the serosal surfaces that could be attributed to therapy. However, in both cases there was diffuse evidence of tumor necrosis within the treated cavity. The only other toxic effect encountered in this trial was nausea and vomiting (Eastern Cooperative Oncology Group grade 2), which occurred following 76% of the treatments. None of the patients demonstrated clinically significant symptoms or signs of neurotoxicity or ototoxicity.

Responses

Table 1 presents the responses of the eight patients. Since evaluation of response in patients with mesothelioma is difficult, a description of each patient's response is included in the table. Only one of the eight patients had unequivocally measurable disease. This patient had a complete response lasting 22+ months. Improvement was clearly evident after just one treatment. Three additional patients had objective improvement as measured by a decrease in volume or complete disappearance of effusions. In all three patients the effusion initially reaccumulated immediately after treatment and then gradually resolved over a period of several weeks: one of these patients (No. 7) became asymptomatic but was found to have residual peritoneal disease after six cycles of treatment; the second patient (No. 5) developed progressive disease after his third cycle of treatment; and the third patient (No. 1) died 4 months after his last course of therapy secondary to progression of disease in his untreated pleural cavity. Three patients with bulky involvement of their pleural or peritoneal cavities failed to respond. However, in one of these patients (No. 3) there was histologic evidence of necrosis along the tumor surface in the treated cavity at autopsy.

DISCUSSION

The most important findings of this study were that: (*a*) intracavitary cisplatin could be safely administered on a weekly schedule; (*b*) a dose of 270 mg/m^2 could be given over 3 weeks with minimal toxicity; (*c*) other than vomiting, toxic effects were minimal and consisted predominantly of myelosuppression; and (*d*) there was suggestive activity against malignant mesothelioma.

There is a large pharmacologic advantage to ip administration of cisplatin (1,3). Following iv administration, delivery of cisplatin to malignant cells is dependent upon capillary blood flow. Capillary perfusion is much less effective in delivering drug to free-floating tumor cells in the peritoneal and pleural cavities or poorly vascularized small serosal nodules than to highly vascularized tissues such as bone marrow or kidney parenchyma. When administered into the pleural or peritoneal cavity, cisplatin, 90 mg/m^2, not only produces peak intracavitary levels that are 20-240 times greater than plasma levels (1,3), but also produces plasma concentration × time exposures which are approximately 50% of those produced by iv administration of similar doses.[6] Thus, following intracavitary administration, cytotoxic concentrations of cisplatin can be delivered to intracavitary tumor by two routes: capillary perfusion and surface permeation. More extensive studies will be required to determine the potential benefit of this approach.

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Phase II Evaluation of Bisantrene in Patients With Advanced Non-Small Cell Lung Carcinoma[1,2]

R. Feld,* W. K. Evans, F. A. Shepherd, G. Deboer, and B. Ottema[3,4]

Fourteen patients with measurable non-small cell lung cancer, who had not received prior chemotherapy, were treated with the anthracene derivative bisantrene. Although treatment was well tolerated, no antitumor activity was observed and all but two patients demonstrated disease progression before the third course of chemotherapy. We conclude that bisantrene does not have significant antitumor activity in non-small cell lung cancer.
[Cancer Treat Rep 69:209–210, 1985]

Bisantrene is one of a series of anthracene dicarboxaldehyde bishydrazone derivatives. It has demonstrated antitumor activity in mouse P388 and L1210 stem cell leukemias and various solid tumor systems including the B16 melanoma, colon tumor 26, and Ridgway osteogenic sarcoma (1). Animal toxicology studies have demonstrated predictable dose-response effects on the hematopoietic and gastrointestinal systems but a notable absence of alopecia and cardiotoxicity (2). In a phase I study, Von Hoff et al (3) found the dose-limiting toxic effect to be myelosuppression and recommended a starting dose of 260 mg/m^2, given as a 2-hour infusion every 3–4 weeks. We conducted a phase II evaluation in patients with non-small cell lung cancer (NSCLC) who had had no previous chemotherapy, to evaluate the antitumor activity of bisantrene in this important tumor type.

PATIENTS AND METHODS

Patients > 18 years of age with pathologically confirmed NSCLC were eligible for study. All patients had measurable disease, an estimated life expectancy of at least 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 3, and evidence of extensive disease (disease extension beyond the primary site and ipsilateral supraclavicular nodes). Patients must not have received any prior chemotherapy; prior radiotherapy was permitted if the course of treatment had been completed at least 4 weeks prior to entry in the study and the patient had at least one measurable lesion outside the radiation field. Adequate hematologic parameters were required for patient entry (granulocyte count > 2000/mm^3, platelet count > 100,000/mm^3), as well as bilirubin < 2 mg/dl, and creatinine < 2.5 mg/dl. Evidence of unstable cardiac arrhythmia, recent myocardial infarction, or significant history of alcohol or drug abuse excluded the patient from study. The protocol was reviewed by the University of Toronto Human Ethics Committee, and all patients gave written informed consent.

Pretreatment Investigation

All patients had a complete medical history, physical examination, evaluation of performance status, and investigations to define the extent of disease. These included cbcs, urinalysis, renal and liver function tests, electrolytes, chest radiograph, electrocardiogram, and, where clinically indicated, liver, bone, or brain scintiscans or skeletal x-rays. All laboratory tests were repeated prior to each course of therapy except the radionuclide scans, which were repeated when clinically indicated to document disease status. Interval blood cell counts were obtained to assess the degree of hematologic toxicity.

Treatment

Treatment with bisantrene was usually initiated at a dose of 260 mg/m^2, and the lyophilized powder was diluted in 5% dextrose and water or 5% dextrose and saline

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[2]Supported by a grant from the Medical Research Division, American Cyanamid Co.
[3]Department of Medicine, Princess Margaret Hospital (*R. Feld* and *B. Ottema*); Department of Medicine, Toronto General Hospital (*W. K. Evans* and *F. A. Shepherd*); and Department of Biostatistics, The Ontario Cancer Institute incorporating the Princess Margaret Hospital (*G. Deboer*), University of Toronto, Canada.
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Reprint requests to: Dr. Ronald Feld, Department of Medicine, Princess Margaret Hospital, 500 Sherbourne St, Toronto, Ontario M4X 1K9, Canada.

to a final concentration of 0.1-0.5 mg/ml. The diluted solution was protected from light and administered within 4 hours of preparation. The treatment was given every 3 weeks as a slow infusion over a minimum of 2 hours, with monitoring of blood pressure every 15 minutes. Two patients started treatment at a dose of 300 mg/m^2. Patients were considered evaluable for response if they received a minimum of two courses of bisantrene separated by at least 3 weeks. In the event of response or stabilization, therapy was to be continued until progression. Dose modifications for hematologic toxicity were incorporated into the protocol.

Response Criteria

Standard cooperative group response criteria were used. The ECOG scale was employed for performance status evaluation, and cooperative group toxicity criteria were used. The drug was discontinued if unacceptable toxic effects occurred, progression of disease took place, or the patient requested it.

RESULTS

Five patients had had previous radiation therapy but none had had previous chemotherapy. All 14 patients treated during this trial were evaluable and none responded. Other patient characteristics and the toxic effects of treatment are shown in table 1. All but two patients had disease progression before the third course of bisantrene therapy. Alopecia occurred in only two patients; phlebitis developed in the vein used for bisantrene administration in three; and nausea and vomiting occurred in only four. Although leukopenia (wbc count < 4000/mm^3) occurred in five patients, no infectious complications were noted. There were two cardiac events observed. One patient developed transient atrial fibrillation while on treatment, which may have been drug-related, and a second patient developed congestive heart failure, probably due to the volume of fluid required for drug administration. There were no drug-related deaths.

TABLE 1.—Patient characteristics

Characteristics	No. of patients (%)
Total	14
Age in yrs	
Median: 54	
Range: 42-79	
Performance status	
Median: 2	
Range: 1-3	
Sex	
Male	11 (79)
Female	3 (21)
Cell type	
Adenocarcinoma	4 (29)
Large cell	5 (36)
Squamous	2 (14)
Poorly differentiated	3 (21)
Prior therapy	
None	9 (64)
Radiation	4 (29)
Combined (surgery and radiation)	1 (7)
Toxic effects	
Drug death	0
Leukopenia (< 4000 cells/mm^3)	5 (35)
Thrombocytopenia (< 130,000 cells/mm^3)	0
Anemia (Hgb < 11.0 g/dl)	4 (29)
Phlebitis	3 (21)
Cardiac	2 (14)*
Nausea or vomiting	4 (29)
Alopecia	2 (14)

* Atrial fibrillation possibly drug-related (1 patient); congestive heart failure, probably due to volume overload (1 patient).

DISCUSSION

Although bisantrene was well tolerated by most patients in the study, no responses were observed in this group of patients who had not received previous chemotherapy. McGuire et al (4) did not observe any responses in 26 evaluable patients with lung cancer treated with bisantrene using the same dose and schedule of drug administration. Other investigators have also failed to observe responses in heavily pretreated patients with NSCLC (5,6). This study of bisantrene in NSCLC confirms the negative results reported by others, and we therefore conclude that bisantrene does not have significant antitumor activity (< 20% response rate with 95% confidence limits) in patients with NSCLC.

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Phase II Study of Cisplatin in Advanced Osteogenic Sarcoma[1]

M. Gasparini,[2,*] J. Rouesse,[3] A. van Oosterom,[4] T. Wagener,[5] R. Somers,[6] J. A. Russel,[7] P. A. Voûte,[8] V. Bramwell,[9] D. Thomas,[10] R. Sylvester,[10] and M. Rozencweig[11]

For the European Organization for Research on Treatment of Cancer Soft Tissue and Bone Sarcoma Group

The activity of cisplatin (CDDP) against advanced osteogenic sarcoma was evaluated in 37 of 50 patients registered by the members of the European Organization for Research on Treatment of Cancer Soft Tissue and Bone Sarcoma Group between 1979 and 1982. All patients had measurable lung metastases. Thirty-one patients (84%) had received previous chemotherapy consisting mainly of high-dose methotrexate, doxorubicin, and vincristine. CDDP (100 mg/m^2) was given as a 24-hour continuous infusion every 3 weeks for a minimum of two cycles, with appropriate fluids and diuretics. In the absence of impairment of the renal function and/or myelosuppression, the dose could be escalated by 20%. The overall response rate was 19% (seven responses among 37 patients), with one complete remission for 51 weeks and six partial remissions from 12 to 26 weeks. The median number of courses of CDDP administered was three, ranging from two to 11. Of 143 courses administered, only 18 (12%) had to be modified because of toxicity. In 16% of the patients some transient impairment of the renal function was observed. CDDP adds to the limited number of chemotherapeutic agents with useful properties in osteogenic sarcoma, and CDDP-containing combination chemotherapy regimens should be actively investigated. [Cancer Treat Rep 69:211–213, 1985]

Cisplatin (CDDP) is a simple coordination compound of bivalent platinum and was the first inorganic antineoplastic agent to enter into clinical investigation, around 1972.

CDDP has shown significant activity against several malignancies, such as testicular, ovarian, and head and neck tumors; bladder carcinoma; and lymphomas (1). In addition, a number of childhood tumors are responsive, with consistent and durable remissions being achieved in yolk sac tumors, neuroblastoma, nephroblastoma, and osteogenic sarcoma (OS) (1–5). The activity in OS is of great interest because of the relative resistance of this tumor to current chemotherapeutic agents. Thus, CDDP has been incorporated in a number of adjuvant regimens for the combined treatment of OS, with encouraging preliminary results (6).

The aim of this phase II study was to estimate the response rate of OS to CDDP and to evaluate toxicity to determine the role of this drug in the management of OS.

MATERIALS AND METHODS

Between 1979 and 1982, a total of 50 patients with metastatic OS were registered by members of the European Organization for Research on Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Three patients were excluded because specimens available for pathologic review were inadequate. Ten additional patients were considered nonevaluable for clinical response because they were lost to follow-up prior to evaluation (five patients), had major protocol violations (two), or received only one course of therapy because of early progression of the disease, early death, and poor

[1]Received Apr 26, 1984; revised Aug 8, 1984; accepted Aug 16, 1984.
[2]Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
[3]Institut Gustave-Roussy, Villejuif, France.
[4]Academisch Ziekenhuis, Leiden, The Netherlands.
[5]Sint Radboudziekenhuis, Nijmegen, The Netherlands.
[6]Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands.
[7]Cancer Clinic, Calgary, Alberta, Canada.
[8]Emma Kinderziekenhuis, Amsterdam, The Netherlands.
[9]Christie Hospital, Manchester, Great Britain.
[10]EORTC Data Center, Brussels, Belgium.
[11]Institut Jules Bordet, Brussels, Belgium.
[*] *Reprint requests to:* Marco Gasparini, MD, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.

general conditions which required surgery (three). Of the 37 evaluable patients, there were 31 males and six females, with a median age of 17 years (range, 9–58). According to the Karnofsky scale, their performance status ranged from 60% to 100% (median, 90%). All patients had lung metastases. Skeletal and subcutaneous deposits were also present in one patient each. Thirty-one patients (84%) had received previous chemotherapy, which consisted mainly of high-dose methotrexate (28 patients), doxorubicin (21), vincristine (15), cyclophosphamide (six), and bleomycin (three). Six patients were previously untreated with chemotherapy. A wbc count > 4000/mm^3, platelet count > 100,000/mm^3, and serum creatinine levels < 1.2 mg/100 ml were required for a patient to be eligible for the study.

CDDP (100 mg/m^2) was administered as a 24-hour continuous infusion and repeated every 3 weeks. In the absence of significant toxicity after the first course, there was provision for dose escalation to 120 mg/m^2 in the subsequent courses. A 20% dose reduction and/or a 1-week delay were applied in subsequent course(s) if creatinine (> 2.5 mg/100 ml) or myelosuppression (wbc count < 2000/mm^3 and/or platelet count < 50,000/mm^3) occurred or if recovery from bone marrow or renal toxicity to pretreatment levels had not occurred by 3 weeks. CDDP was administered in 4000 ml of 5% dextrose in 0.45 saline plus 6 g of KCl and 48 g of mannitol. In addition, the 24-hour CDDP infusion was preceded by a 4-hour infusion of 1000 ml of 5% dextrose and followed by a 24-hour infusion of 3000 ml of 5% dextrose plus 12 g of mannitol. If urine output fell to < 100 ml/hour, 20–40 mg of furosemide was administered.

At least two courses of CDDP were required to consider the patient evaluable. Complete response (CR) was defined as the complete disappearance of all symptoms and signs of disease for a minimum of 4 weeks. Partial remission (PR) was defined as a > 50% reduction of the product of the two largest perpendicular diameters of measurable lesions for a minimum of 4 weeks. Stable disease was defined as a < 50% reduction or a < 25% increase of measurable lesions. Progressive disease was defined as the appearance of new lesions or a > 25% increase in any lesion.

RESULTS

The overall response rate (CR + PR) was 19% in the 37 patients. One patient had CR of multiple lung metastases for 29 weeks (51 from start of treatment). Six patients achieved PR for 5–20 weeks (12–26 from start of treatment). Five of seven responders had been previously treated with multiple-drug chemotherapy including doxorubicin, high-dose methotrexate, and vincristine. All of the responsive patients were in their second decade of life. Clinical response always began after the first two cycles of therapy. If the disease remained stable after two cycles, additional treatment never achieved a clinical objective response. The Karnofsky status was not related to the clinical response; three of seven responders were initially classified as having ≤ 70%.

The median number of courses of CDDP given was three, ranging from two to 11. Eight patients received six or more courses. The median dose per course was 100 mg/m^2 (range, 84–118) and the median cumulative dose administered was 320 mg/m^2 (range, 181–1009).

Because toxicity was never severe, it was not necessary to discontinue therapy because of side effects. Of the total number of 143 courses administered, only 18 (12%) were modified either by reducing the dose of CDDP or by delaying the scheduled administration by 1 week because of toxicity. This comprised leukopenia (nine courses), mild creatinine elevation (seven), both leukopenia and mild creatinine elevation (one), and ototoxicity (one). Six of 37 patients (16%) showed transient creatinine elevation, which was > 2.5 mg/100 ml in only two. A clinical hearing loss was observed in 16% of the patients.

DISCUSSION

This large-scale phase II study confirms the activity of CDDP against advanced OS. The overall response rate was 19% in 37 patients. Our data in chemotherapy-naive patients (two PRs among six patients) were particularly favorable but small sample size precludes firm conclusions. In a fairly large proportion of patients (32%), stabilization of disease progression was obtained for > 3 months.

Most published data on CDDP in OS have been obtained in far-advanced, extensively pretreated patients. Baum et al (4) reported two PRs and one CR in a series of 17 pediatric patients using CDDP at a similar dose administered over an 8-hour period. Ochs et al (3) reported three PRs and one CR in eight previously treated patients, using various dose schedules. In a group of 13 patients Pratt et al (7) had one CR and one PR with 2-hour infusions at 30 mg/m^2 once weekly and 90 mg/m^2 once every 3 weeks, respectively.

A higher response rate (57%) was obtained by Jaffe et al (8) by giving CDDP intra-arterially as first-line chemotherapy to treat the primary tumors of seven patients with OS.

In our series, previous chemotherapy with high-dose methotrexate and/or doxorubicin did not prevent a clinical response to CDDP. Similarly, Rosen et al (9) observed a 20% overall response rate in 20 patients with advanced OS failing after intensive chemotherapy with high-dose methotrexate, doxorubicin, and a combination of bleomycin, cyclophosphamide, and dactinomycin. These observations indicate that CDDP is not

cross-resistant with other drugs widely used in the management of OS. As a consequence, combining CDDP with other active drugs may increase remission rates in advanced OS, and suitable combinations would be worth testing in an adjuvant or neoadjuvant (10) setting. Preliminary results of combination chemotherapy including CDDP have been published and are promising (6,11,12).

CDDP adds to the limited number of chemotherapeutic agents which have useful activity in OS. The optimal schedule of administration and appropriate selection of other agents for the combination treatment of primary OS represent a field of current and future clinical investigations.

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Phase II Trial of Diaziquone in Patients With Colon Cancer[1]

James A. Neidhart,[2] Charles Erlichman,[3] Francisco Robert,[4] Enrique Velez-Garcia,[5] John F. Bender,[6,*] and Antonio J. Grillo-López[6]

Seventeen patients with metastatic colon cancer received diaziquone iv daily for 5 days repeated every 28 days. Based on recommended starting doses for phase II trials (6–8 mg/m² daily × 5), the first six patients received 7 mg/m²/day × 5. Two of these patients were heavily pretreated with chemotherapy, two had received prior 5-FU alone, and two had received no prior chemotherapy. There were no responses and three septic deaths (both of the heavily pretreated patients and one 5-FU-only patient who received concurrent radiotherapy). Eleven subsequent patients received 5.5 mg/m²/day × 5. Nine had no prior therapy; two had received prior 5-FU. No antitumor responses were observed. Myelosuppression was again the major toxic effect. No further septic deaths occurred. Diaziquone in this dose and schedule had no antitumor activity in this group of patients. [Cancer Treat Rep 69:215–217, 1985]

Diaziquone (AZQ) is a rationally designed antitumor agent (1). It possesses characteristics thought necessary for crossing the blood-brain barrier: excellent lipid solubility, low degree of ionization, and relatively low molecular weight (2). It has shown a broad spectrum of activity against a wide variety of murine tumor systems including curative activity against intracerebrally implanted L1210 leukemia and ependymoblastoma (1). Although the exact mechanism of action is not known, the aziridinyl group is an alkylating function and may be responsible in part for the observed antitumor activity (3). Generation of a free radical and the subsequent production of superoxide may also be involved in the cytotoxic effect of the drug (4). Following iv administration, plasma disappearance was very rapid with a disposition half-life of 2–6 minutes and an elimination half-life of 25–35 minutes (5).

AZQ rapidly penetrates the central nervous system, reaching peak concentrations (30%–50% of corresponding plasma levels) in approximately 1 hour (6). It would appear that AZQ is extensively metabolized in man, and that very little of the parent compound is excreted unchanged. The dose-limiting toxic effect in phase I trials has been myelosuppression (1). Thrombocytopenia is often severe. Based on recommended starting doses of 6–8 mg/m² day × 5 (7), a phase II trial of AZQ in patients with colon cancer was initiated.

MATERIALS AND METHODS

Patients between the ages of 18 and 80 years (males or nonpregnant females) with histologic evidence of colon cancer refractory to conventional therapy were eligible. Additional requirements were: (*a*) expected survival > 4 weeks; (*b*) performance status (Zubrod scale) of 3 or greater (later upgraded to 2 or better); (*c*) adequate time to recover from prior chemotherapeutic or radiation-induced toxicity; (*d*) absolute granulocyte count > 1500/mm³ and a platelet count > 100,000/mm³ (later increased to 150,000/mm³); and (*e*) measurable disease with evidence of progression. Patients were excluded from entry if they had: (*a*) a history of treatment with any other phase I or II investigational agent; (*b*) more than one primary malignancy; (*c*) impaired hepatic function (bilirubin > 1.5 mg/100 ml, SGOT ⩾ 60 units/ml) or impaired renal function (creatinine > 2 mg/100 ml); or (*d*) conditions which would require the use of concurrent systemic, intracavitary, or intrathecal chemotherapy or radiotherapy. Patients were informed of the investigational nature of the study and gave written informed consent.

AZQ was initially administered at a dose of 7

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[2]The Ohio State University Comprehensive Cancer Center, Columbus.
[3]The Princess Margaret Hospital, Toronto, Canada.
[4]Veterans Administration Hospital, San Juan, Puerto Rico.
[5]University of Puerto Rico, School of Medicine, San Juan.
[6]Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Clinical Oncology Research Program, Ann Arbor, MI.
[*]*Reprint requests to:* Dr. John F. Bender, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, 2800 Plymouth Rd, Ann Arbor, MI 48105.

mg/m²/day for 5 days every 4 weeks. Patients not achieving a granulocyte count nadir between 1000 and 1500/mm³ received a 20% dosage increase (providing that the platelet count nadir was > 75,000/mm³). Patients with granulocyte count nadirs ≤ 1000/mm³ or platelet count nadirs ≤ 75,000/mm³ received a 20% dosage reduction. Subsequent courses were delayed until full hematologic recovery (granulocytes ≥ 1500/mm³, platelets ≥ 100,000/mm³) had occurred.

During therapy, patients were evaluated with history, physical examination, performance status, chest x-ray, ECG, glucose, BUN, total protein, albumin, calcium, SGOT, LDH, alkaline phosphatase, uric acid, bilirubin, serum creatinine, serum electrolytes, urinalysis, and tumor measurements. Applicable x-rays or scans were obtained. Cbc and platelet counts were done weekly. Response criteria were as follows: *complete response*—the disappearance of all measurable tumors; *partial response, good*—a > 50% decrease in the sum of the products of the perpendicular diameters of measurable tumors; *partial response, fair*—a 25%-50% decrease in the sum of the products of the perpendicular diameters of measurable tumors; and *no response*—any response not meeting the above criteria and any development of new tumors. The duration of response was calculated from the onset of response to the documentation of progression.

RESULTS

Seventeen patients with metastatic colon cancer received AZQ iv daily for 5 days repeated every 28 days (table 1). The first six patients received 7 mg/m²/day × 5. Three of these first six patients (both of the heavily pretreated patients and one 5-FU-only patient who received concurrent radiotherapy) experienced severe bone marrow suppression with mean platelet count and granulocyte count nadirs of 9000/mm³ (range, 5000-15,000) and 160/mm³ (range, 20-240), respectively. All three patients subsequently died of sepsis following drug-induced myelosuppression. The initial dosage was decreased by 20%, and 11 patients subsequently received 5.5 mg/m²/day × 5 as initial therapy. Nine of these 11 patients had received no prior chemotherapy (four of the nine had received prior radiotherapy) and the other two had received 5-FU only. No further septic deaths occurred. Myelosuppression was again the major toxic effect. Hematologic toxicity induced by AZQ is illustrated in table 2. No evidence of renal, hepatic, or neurologic toxicity was observed. There were no complete or partial responses noted in this study.

TABLE 1.—Patient characteristics

Characteristics	Initial dose	
	7 mg/m²	5.5 mg/m²
No. of patients	6	11
Sex		
Males	0	7
Females	6	4
Age (yrs)		
Median	53	53
Range	30-73	46-74
Performance status		
Median	1	1
Range	0-3	0-2
Prior therapy *		
None	1	5
RT only	1	4
Cx only	2	2
RT and Cx	2	0

* RT = radiotherapy; Cx = chemotherapy.

TABLE 2.—Hematologic toxicity of AZQ

Characteristics	Dose			
	7 mg/m²/day		5.5 mg/m²/day	
	Course 1	Course 2	Course 1	Course 2
No. of patients	6	1	11	10 *
Lowest neutrophil count ×/10³				
Median	1.6	2.4	2.6	2.6
Range	0.02-5.4	2.4	0.4-6.1	0.5-6.3
Day (median)	21	21	23	16
% < 1.0	66	0	27	22
% < 0.5	50	0	18	0
Lowest platelet count ×/10³				
Median	66	61	154	138
Range	5-216	61	28-401	59-309
Day (median)	19	21	22	18
% < 100	83	100	40	44
% < 50	66	0	20	0

* 6 of these 10 patients required a 20% dosage reduction for Course 2 (ie, 4.4 mg/m²/day). A 7th patient's dose was unchanged, and the remaining 3 patients were able to receive a 20% dosage increase.

DISCUSSION

It became apparent early in this multicenter trial that the initial dose of 7 mg/m^2/day for 5 days was too high. Even after a dosage reduction was imposed on all further patient accession, myelosuppression (thrombocytopenia in particular) was severe in some patients. It is curious to note how variable this effect was, even in the lightly pretreated and untreated patients. Since AZQ is extensively metabolized in the liver, hepatic impairment might be expected to enhance its toxic effect. Although all of these patients had bilirubin and transaminase levels within the normal range as prerequisite for entry on study, virtually all patients had hepatic involvement with tumor at the time of treatment with AZQ. Since this drug has such a short half-life ($t_{1/4}\beta \cong$ 25–35 minutes) and steep dose-toxicity curve, one could postulate that even slight alterations in its pharmacokinetic disposition might translate to major clinical effects.

AZQ in this dose and schedule had no antitumor effect in this group of patients. With no responses in 11 patients previously untreated with chemotherapy, the probability that AZQ would have an actual response rate of 25% is $< 5\%$.

For all future trials of AZQ in other tumor categories utilizing a 5-day schedule, we recommend an initial starting dose of 5.5 mg/m^2.

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NMU-1, a New Transplantable Mouse Lung Tumor: Biological and Chemosensitivity Properties In Vivo[1]

Graziella Pratesi,* Gabriella Pezzoni, and Giorgio Parmiani[2,3]

NMU-1 is a lung adenocarcinoma induced by *N*-nitroso-*N*-methyl-urea in a BALB/c Lac Dp mouse and maintained in vivo by sc passages of tumor fragments. No spontaneous regressions have been observed. After sc implantation, NMU-1 metastasizes to the lung as shown by a bioassay. Seven established antitumoral drugs were used to evaluate the chemosensitivity of this neoplasm. Mitomycin, cyclophosphamide, and cisplatin statistically affected tumor growth, as evaluated by three end points (ie, tumor weight, increase in lifespan, and tumor growth delay). 5-FU, doxorubicin, and vincristine showed significant activity on two end points. Carmustine did not affect any end points. [Cancer Treat Rep 69:219–221, 1985]

Since chemical compounds are known to be involved in human lung carcinogenesis (1), attention has been focused on developing and studying lung tumors induced by chemicals in laboratory animals used as models for biological studies and for preclinical evaluation of anticancer agents.

In our laboratory, a tumor line designated as NMU-1 has been established from a lung adenocarcinoma induced in a BALB/c male by *N*-nitroso-*N*-methyl-urea (NMU), a direct alkylating agent known to induce different tumor types in various species of animals (2). The aim of this paper is to report the biological characteristics of this tumor line and its sensitivity to some clinical antitumor drugs.

MATERIALS AND METHODS

All of the mice used throughout the study weighed 18–22 g and were provided by the Charles River Breeding Laboratories (Calco, Italy) or by the animal colony of our Institute.

The lung tumor described in the study was derived from a 50-week-old BALB/c Lac Dp male mouse treated with a single ip injection of 25 mg/kg of NMU (Sigma Co, St. Louis, MO) dissolved in 10 mM citrate buffer, pH 6.0, when 1 week old. The tumor line was maintained by serial sc passages of small tumor fragments (about 20 mg) in BALB/c males.

The NMU-1 metastasizing capacity in many organs was tested by bioassay 28 days after sc tumor implantation (3). Recipient mice were observed for 100 days.

For chemotherapy studies, BALB/c male mice were injected with fragments of NMU-1 by trocar. Seven antitumor drugs, currently available for clinical use, were given iv in a volume of 10 ml/kg of body weight once a week for 4 weeks starting the day after the tumor inoculum. Toxicity was evaluated in tumor-bearing animals as the number of mice dying either before the first control mouse or after the first control mouse with a small tumor (< 1 g) and reduced organs. Three end points were used to assess antitumor activity: (*a*) 100 × tumor weight in treated/control mice (% T/C) according to Geran et al (4); (*b*) percent increase in lifespan of the treated mice as compared to the control mice (% ILS), given by 100 × (median survival time [MST] of treated mice minus MST of control mice/MST of control mice); and (*c*) delay in tumor growth (T - C), calculated as the difference in number of days required for the tumors to reach 1 g in treated and control mice (< 7 days was considered inactive). The Student's t test was used to calculate the statistical significance of the first two parameters.

RESULTS

The primary tumor has been characterized as an

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[2]Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

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*Reprint requests to: Dr. Graziella Pratesi, Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.

TABLE 1.—Growth properties of NMU-1 tumor implanted sc in BALB/c male mice

Inoculum level (No. of cells/mouse)	Mice with tumor/ total No.	AT* of tumor appearance	Doubling time†	Days to reach 600 mg	MST in days (range)
10^5	10/10	31.5 (22-44)	3.5	35.5	68.5 (65-115)
10^6	10/10	27.2 (19-44)	3	31.5	69.5 (60-85)
10^7	10/10	17.0 (17)	4	20.5	50.0 (47-86)
Fragments	53/55	7.4 (6-10)	3	12.0	36.0 (20-62)

*AT = average time in days (range).
†Doubling time = days required for tumor to grow from 300 to 600 mg.

alveologenic-bronchiolar carcinoma with areas of papillary gland pattern. This type of structure has been preserved after as many as 18 syngeneic sc passages. The sc inoculation of NMU-1 into BALB/c mice of both sexes resulted in the growth of a thinly encapsulated nodular mass which led to death of the animals when its weight was ⩾ 10 g. Table 1 reports some parameters related to tumor growth in BALB/c male mice injected with serial dilutions of tumor cells or with tumor fragments. Tumors were provided with as few as 10^5 cells/mouse. In the CD2F1 hybrid mice, all of which developed tumors, the tumor growth pattern was similar to that observed in BALB/c mice. Tumors did not grow in allogeneic C3H/He and C57BL/6J mice.

For detection of metastatic cells, BALB/c mice were implanted sc with brain, lungs, liver, spleen, and kidneys from donor mice implanted with NMU-1 28 days previously: one of 20 of the brain-recipient mice and 17 of 20 of the lung-recipient mice developed growing tumors.

Table 2 shows the effects on the three antitumor activity parameters given by the optimal dose of each tested drug (three dose levels were tested for each drug). Carmustine was ineffective on the three parameters. All of the other drugs statistically affected tumor weight at $P < 0.01$. Moreover, vincristine and doxorubicin were slightly effective on growth delay, whereas 5-FU statistically affected the ILS. Cisplatin caused a remarkable growth delay (30 days) but it was ineffective on survival time, probably because of its toxicity (four of ten mice). In a second experiment in which the same dose was well-tolerated, cisplatin displayed a significant activity on survival time together with a slight effect on tumor growth delay. Mitomycin had a statistically significant effect on the two parameters, mainly increasing the survival time. Cyclophosphamide also displayed a statistically significant increase of the two parameters.

DISCUSSION

The growth properties of the sc implanted NMU-1 tumor, an alveologenic-bronchiolar adenocarcinoma, were similar in syngeneic BALB/c and in first-generation hybrid mice but not into H-2 incompatible animals, thus indicating that NMU-1 cells regularly express their major histocompatible antigens. The tumor was also able to spontaneously metastasize to the lung in most of the mice (17 of 20).

To evaluate the chemosensitivity pattern of the NMU-1, seven clinically available antitumor drugs of different classes were tested according to the same treatment schedule. Three different end points were observed, ie, tumor weight, ILS, and tumor growth delay.

Carmustine was inactive on all three parameters. Because the other tested drugs statistically reduced tumor weight, this parameter seemed poorly predictive of the activity on human lung cancers. The other two parameters reported for antitumor activity could better correlate with the activity on human cancers. In fact, mitomycin, cyclophosphamide, and cisplatin, three drugs showing a certain degree of activity as single agents on human lung tumors (5,6), significantly modified both these parameters.

TABLE 2.—Chemosensitivity of lung tumor NMU-1

Transplant generation	Drug	Dose (mg/kg)	Toxicity (No. of deaths/total treated)	% T/C*	% ILS	T - C (days)
9	Carmustine	19.2	0/9	56	-1	4
9	Vincristine	1.5	1/10	22†	5	8
5	Doxorubicin	7.7	1/9	24†	7	10
16	5-FU	66	0/8	41†	38†	5
5-9	Cisplatin	5.9	4/10-0/9	3†-28†	1-25†	30-8
16	Mitomycin	4	1/8	14†	131†	12
5	Cyclophosphamide	100	1/9	10†	28†	19

*Tumor weight was calculated on the 26th, 23rd, and 24th day of the experiments done at the 5th, 9th, and 16th transplant generation, respectively.
†$P < 0.01$ as compared to the control groups by Student's t test.

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Mitomycin and Methotrexate: Negative Experience in Untreated Colorectal Carcinoma[1,2]

J. C. Wernz, A. K. Kao, F. M. Muggia,* and R. F. Asbury[2]

Mitomycin (Mit-C) and methotrexate (MTX) when used alone have shown some activity in colorectal cancer (1). In vitro synergism (2) of these agents in L1210 murine leukemia further supported clinical trials with this combination. However, in patients previously treated with chemotherapy the combination was ineffective (3). This trial was therefore designed to include only untreated patients.

Eligibility criteria included histologic confirmation of measurable metastatic or unresectable colorectal adenocarcinoma, no prior treatment other than surgery, expected survival of at least 60 days, and informed consent. All patients were to be at least 2 weeks postoperative and free of infection. Required laboratory values included: wbc count $\geq 4 \times 10^3/mm^3$, platelet count $\geq 10^5/mm^3$, hemoglobin ≥ 10 g/100 ml, BUN ≤ 25 mg/100 ml, creatinine ≤ 1.5 mg/100 ml, total bilirubin ≤ 2.0 mg/100 ml, and creatinine clearance of at least 65 ml/minute.

Initial doses were 10 mg/m^2 of Mit-C every 6 weeks and 60 mg/m^2 of MTX (40 mg/m^2 in patients with a poor performance status) iv every 2 weeks; doses were adjusted to tolerance. Leucovorin rescue was not deemed necessary with this preselection of patients. Standard methods were used to assess responses.

Of 24 patients entered in the study, 13 were males and 11 were females. The median age was 65 years (range, 52–76), and the Eastern Cooperative Oncology Group performance status was 1 (range, 0–4). All patients were evaluable for toxicity. Three patients were excluded from response evaluation: two due to early withdrawal secondary to protocol-related complications, and one due to intestinal obstruction early in the first cycle. One patient died on Day 12 of Cycle 1 from treatment-related sepsis, pneumonia, and renal failure. Another patient was removed from study after 20 days due to life-threatening uremia. Treatment was discontinued in the third patient when tumor progression resulted in intestinal obstruction before Day 14 of the first cycle and subsequent non-protocol-related death. All other patients received a median of two cycles, with a median total dose of 31 mg (range, 15–97) of Mit-C and 520 mg (range, 120–1742) of MTX.

Objective partial responses occurred in two patients (10% response rate; 90% confidence limits, 2%–28%), with a median response duration of 3.5 months. The median survival for all patients was 44+ weeks.

The regimen proved to be very toxic. Anemia (hemoglobin ≤ 10 g/100 ml), leukopenia (wbc count $\leq 4000/mm^3$), and thrombocytopenia (platelet count $\leq 130{,}000/mm^3$) developed in 67%, 63%, and 75% of the patients, respectively. The median nadir and ranges were 9.7 g/100 ml (8.1–11.4), $2.9 \times 10^3/mm^3$ (0.4–4.8), and $100 \times 10^3/mm^3$ (11–398), respectively. Two patients developed life-threatening hematologic toxic effects (wbc count $< 1.0 \times 10^3/mm^3$ and platelet count $< 25 \times 10^3/mm^3$). Seven packed rbc transfusions and four platelet transfusions were required. One death due to sepsis complicated by decreased creatinine clearance and stomatitis was recorded. Seventy-five percent of the patients developed at least moderate subjective gastrointestinal intolerance and stomatitis. Mit-C extravasation resulted in serious tissue necrosis in three patients, all of whom required plastic surgery. MTX caused a severe skin rash in one patient. Presumed Mit-C-induced pulmonary toxicity led to respiratory difficulty in three patients.

In conclusion, this trial did not demonstrate in vivo synergism between Mit-C and MTX, and the combination proved very toxic even in previously untreated patients with disseminated colorectal cancer. Such severe and unpredictable toxic effects were also reported by others (4,5) in other disease states.

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*Reprint requests to: F. M. Muggia, MD, New York University Medical Center, School of Medicine, The Rita and Stanley H. Kaplan Cancer Center, 550 First Ave, New York, NY 10016.

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Treatment of Relapsed Non-Hodgkin's Lymphoma With a Combination of Hydroxyurea, Ifosfamide, and Etoposide[1]

A. B. Gasser,[2,3] W. P. Steward,[2,*] J. Wagstaff,[2] J. H. Scarffe,[2] and D. Crowther[2]

Among drugs used for second-line treatment of non-Hodgkin's lymphoma (NHL), those with the highest single-agent response rates are ifosfamide (1) and etoposide (2). Response is improved by using these drugs in combination regimens (3,4).

Hydroxyurea (HU), a phase-specific cytotoxic agent, has been used for cell synchronization (5). Ifosfamide and etoposide were given after oral HU to patients with relapsed NHL in the hope that use of this potential synchronizing agent might improve the response rate.

PATIENTS AND METHODS

Nineteen patients (ten in second relapse, nine in third relapse or disease progression) with NHL of "high-grade" pathology were treated.

The hydroxyurea, ifosfamide, and etoposide regimen (HIV) was given every 3 weeks and comprised eight oral doses of HU, 1 g every 6 hours (Days 1 and 2), and ifosfamide, 3 g/m^2, and etoposide, 80 mg/m^2, both given iv 24 hours after the last dose of HU (Day 4) with 3 L of normal saline hydration and mesna. Etoposide (80 mg/m^2) was given iv on Day 5 and orally (160 mg/m^2) on Day 6. Only 1 night as an inpatient was necessary for each treatment. Therapy was discontinued if there was disease progression or unacceptable toxicity.

TABLE 1.—Patient and study characteristics*

Age (yrs)	
Median	50
Range	15-68
Sex	
Male	9
Female	10
Clinical stage	
IIIB	2
IVB	17
Bone marrow involved	9
Liver involved	8
Prior radiotherapy	13
No. of previous chemotherapy regimens/patient	
Median	3
Range	2-6
Response	
Complete	1
Partial	9
Static	3
Duration of response (mos)	
Median	4
Range	2-19
Survival after study entry (mos)	
Median	6
Range	2-21

*Unless otherwise specified, values = No. of patients.

RESULTS

Patient characteristics and response are shown in table 1. Each patient received a median of three cycles (range, two to six). One complete remission (10.5 months' duration) and nine partial remissions (overall response rate, 53%) occurred. Bone marrow toxicity was moderate. The nadir neutrophil count fell less markedly with each course given, being < 1000/μl in seven patients after the first cycle (during which four severe infections requiring parenteral antibiotics occurred) and in only one after the third. Three infections requiring oral antibiotics occurred after the second and third cycles. Dose reductions of 25% were made for subsequent courses in patients experiencing severe infections. There were no treatment-related deaths.

DISCUSSION

The response rate for HIV compares favorably with the response rates for the drugs used as single agents. It is

[1]Received Apr 26, 1984; revised Aug 20, 1984; accepted Aug 27, 1984.

[2]Cancer Research Campaign, Department of Medical Oncology, Christie Hospital and Paterson Laboratories, Manchester, United Kingdom.

[3]*Present address:* Klinisches Tumorregister, Inselspital, Bern, Switzerland.

Reprint requests to: Dr. W. P. Steward, Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Wilmslow Rd, Manchester M20 9BX, United Kingdom.

similar to the response rate for other combinations (4), though lower than that reported for ifosfamide, etoposide, and methotrexate (3). Although HIV provided useful palliation of symptoms (80% of patients reporting a significant improvement of performance status) with acceptable toxicity, the durations of responses were short. There is no evidence that the addition of HU gave better results than would be expected from a combination of ifosfamide and etoposide alone.

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Failure of 5-Day Vinblastine Infusion in the Treatment of Patients With Renal Cell Carcinoma[1]

I. F. Tannock[2,*] and W. K. Evans[3]

Renal cell carcinoma seldom responds to anticancer drugs, but rare responses have been reported following treatment with bolus injections of vinblastine (1). Following a report that vinblastine by 5-day infusion led to responses in patients with heavily treated metastatic breast cancer (2), we have studied the same treatment in patients with cancer of the breast and in patients with cancer of the kidney. We were unable to confirm activity of this treatment in 17 patients with heavily treated breast cancer (3), and this report describes our similar experience in 14 patients with renal cell carcinoma.

PATIENTS AND METHODS

There were eight men and six women from 40 to 65 years of age (median, 58). Twelve patients had a tissue diagnosis of renal cell carcinoma and the other two had a typical vascular tumor in the kidney demonstrated by arteriography and metastases in the lungs. All patients had bidimensionally measurable disease: 13 in the lungs (± other sites) and one in multiple subcutaneous sites (± bone). Most patients had had prior treatment with hormones (usually medroxyprogesterone acetate), but only two had received prior chemotherapy with oral methotrexate. No patient had responded to prior treatment. Performance status (Eastern Cooperative Oncology Group scale) was 1 in four patients; 2 in nine; and 3 in one.

Patients were admitted to hospital for treatment, and received vinblastine, 1.5 mg/m^2/day as a 5-day continuous infusion. Treatment was repeated at 3-week intervals, and in some patients the dose was increased to 1.7 mg/m^2/day. Three patients received only one course, five patients received two, and the others received from four to 11. Since this trial sought to assess patient benefit, all patients are included for analysis.

RESULTS

On the basis of a study of measurement error we have recently recommended the use of stringent response criteria in trials designed to assess patient benefit (4) and intended to use such criteria in analyzing the current trial. However, we observed no patient who satisfied even the definition of partial response in most common usage (ie, shrinkage by 50% of the sum of cross-sectional areas of index lesions, without progression of nonmeasurable lesions, for a minimum of 1 month).

Twelve of the patients had clear evidence of progression on treatment. One patient had slight shrinkage of pulmonary nodules during six courses of treatment and had improvement in dyspnea and activity level which lasted for 11 months. Her disease progressed when treatment was restarted, and the role of chemotherapy in palliating her disease remains uncertain. One patient had a mixed response. She had complete disappearance of pulmonary metastases and supraclavicular nodes, with improvement in dyspnea following three courses of treatment; however, she developed new and enlarging bone lesions while on treatment and required radiotherapy and pinning of a femur. She received further treatment recently for recurrent pulmonary metastases at 20 months after initial vinblastine treatment, but these lesions have not responded to treatment.

Most patients tolerated treatment with mild discomfort. Venous irritation requiring replacement of the iv line occurred frequently. Only four patients complained of nausea and two had vomiting. Severe myelosuppression (< 100 polymorphonuclear neutrophils/mm^3) occurred in two patients, but there were no clinical sequelae and no thrombocytopenia. In only one patient was treatment discontinued because of possible toxicity. This woman, with a history of coronary artery disease, developed acute coronary insufficiency after 3 days of treatment. She received no further vinblastine and died 2 months later of metastatic disease.

Initiation of treatment using 5-day infusion of vinblastine in 14 patients with metastatic renal cell carcinoma yielded no major responses. A true response rate > 20% is thus excluded at the 95% confidence level (5). Vinblas-

[1]Received June 26, 1984; revised Aug 31, 1984; accepted Sept 12, 1984.
[2]Department of Medicine, Ontario Cancer Institute, Toronto, Canada.
[3]Department of Medicine, Toronto General Hospital, Ontario, Canada.
*Reprint requests to: Dr. I. F. Tannock, Department of Medicine, Ontario Cancer Institute, 500 Sherbourne St, Toronto, Ontario, Canada M4X 1K9.

tine by 5-day infusion cannot be recommended for treatment of renal cell carcinoma.

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Phase II Study of 5-Day Infusion of Vinblastine in Patients With Advanced Ovarian Carcinoma[1,2]

Mukund K. Shah, Karen St. Marie, Robert B. Catalano, Kathleen Dierks, and Richard H. Creech[3,4,*]

Intermittent therapy with vinblastine has not been found to be effective in the treatment of advanced ovarian carcinoma. Two of 18 patients receiving intermittent vinblastine in three series had responses (1-3). Recently, Yap et al (4), utilizing a 5-day infusion of vinblastine in patients with refractory advanced breast carcinoma, have found a 40% complete and partial response rate in 30 evaluable patients. This study was developed to determine whether the potentially more effective 5-day infusion of vinblastine has any antineoplastic activity in patients with alkylating agent- and cisplatin-refractory ovarian carcinoma.

PATIENTS AND METHODS

Sixteen patients with advanced measurable or evaluable ovarian carcinoma refractory to alkylating agent (melphalan) and cisplatin chemotherapy were entered and evaluable in a trial of vinblastine given by subclavian vein at a dose of 1.6 mg/m^2/day for 5 days every 3-4 weeks as suggested by Yap et al (4). The response criteria and toxicity were classified according to standard Eastern Cooperative Oncology Group (ECOG) criteria (5). Age, interval from diagnosis to initiation of vinblastine, ECOG performance status, pathologic classification, stage at diagnosis, response to previous therapy, and number of previous chemotherapy regimens are summarized in table 1.

TABLE 1.—Characteristics of 16 vinblastine-treated patients

Characteristic	No. of patients
Age (yrs)	
Median: 59	
Range: 34-76	
Interval from diagnosis to vinblastine (mos)	
Median: 20	
Range: 12-75	
ECOG performance status	
1	1
2	8
3	5
4	2
Pathologic classification	
Poorly differentiated adenocarcinoma	8
Papillary serous cystadenocarcinoma	6
Mucinous cystadenocarcinoma	1
Clear cell carcinoma	1
Stage at diagnosis	
I	1
II	3
III	11
IV	1
Responses to previous therapy	
Pelvic irradiation	1 adjuvant
Melphalan	7 adjuvant
Melphalan	3/9
Cisplatin-containing regimens	6/16
Mitomycin	0/14
Other chemotherapy	0/5
No. of previous treatment regimens	
2	2
3	11
4	2
6	1

RESULTS

No patient had a complete or partial response. Seven stable patients had a median survival of 5 months (range, 3-7). Nine patients with progressive disease had a median survival of 3 months (range, 1-5). The median survival for patients with a performance status of 1, 2, and 4 was 5 months; for patients with a performance status of 3, median survival was 3 months.

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[3]Department of Medicine, American Oncologic Hospital, The Fox Chase Cancer Center, Philadelphia, PA.

[4]We thank Robert Goldberg-Alberts for statistical assistance.

Reprint requests to: Richard H. Creech, MD, American Oncologic Hospital, The Fox Chase Cancer Center, Central and Shelmire Aves, Philadelphia, PA 19111.

Three patients required rbc transfusions because of anemia. No patient had a wbc count < 3000/mm^3. One patient each had a platelet count < 90,000/mm^3, generalized body aches, alopecia, and a reversible pneumothorax after placement of a subclavian catheter.

DISCUSSION

Although the vinca alkaloids have not been known to have significant activity against ovarian cancer, it was hoped that Yap's infusion method of vinblastine therapy would offer a possibly effective schedule for induction of responses in chemotherapy-refractory patients. Although the patients studied had previously failed at least two chemotherapy regimens, their survival of 1-7 months allowed sufficient time to evaluate toxicity and therapeutic response. It is concluded that infusion of vinblastine at 1.6 mg/m^2/day for 5 days every 3-4 weeks does not have significant antineoplastic effect against previously treated ovarian cancer and that further study is not warranted.

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Phase II Trial of Mitoxantrone in Advanced Sarcomas: A Southwest Oncology Group Study[1,2]

Frances E. Bull,[3] Daniel D. Von Hoff,[4] Stanley P. Balcerzak,[5] Ronald L. Stephens,[6] and Frank J. Panettiere[7,*]

Currently, doxorubicin as a single drug, or as the primary drug in combination therapy, is the mainstay of therapy for adult patients with advanced sarcomas. Mitoxantrone is an anthraquinone derivative, active in animal tumor screens, with less cardiotoxicity in animals than doxorubicin. A lack of cross-resistance with doxorubicin has been demonstrated in carcinoma of the breast (1,2). Seeking evidence of activity and lack of cross-resistance in advanced sarcoma as well, the Southwest Oncology Group (SWOG) undertook a phase II trial of mitoxantrone in adult patients with advanced sarcomas, who had previously received doxorubicin either as a surgical adjuvant or as therapy for advanced disease. Substantial numbers of patients with both boney sarcomas and a variety of soft tissue sarcomas were sought, since important variation in response rates related to cell type, site of origin, and metastatic sites has been suggested in several recent reports (3-6).

METHODS

Patients were eligible if they had: histologically proven, measurable, incurable soft tissue or boney sarcoma; life expectancy of at least 6 weeks; performance status of ≤ 3 by SWOG criteria; wbc count $\geq 3500/mm^3$; platelet count $\geq 125{,}000/mm^3$; serum creatinine ≤ 2.0 mg/100 ml; and bilirubin ≤ 2.0 mg/100 ml. Recovery from the toxicity of any prior chemotherapy was required, and informed consent had to be given.

Mitoxantrone was given as an iv infusion in 100 ml of 5% dextrose in water over 30 minutes. The initial dose was 12 mg/m^2, repeated every 3 weeks. A 10% dose escalation occurred if no hematologic toxicity was recorded; a 17% dose reduction occurred if the wbc count nadir was $< 2000/mm^3$; a nadir of 2000-3999/mm^3 was sought. An adequate trial was two courses or rapid progression of disease after one course. Patient accrual to this study stopped just prior to the reports of possible cardiotoxicity due to mitoxantrone. All patients who were still on study were required to have normal ECG and ejection fraction prior to each subsequent dose. This monitoring involved a minority of the patients studied.

RESULTS

Patient characteristics are recorded in table 1. There were 11 nonevaluable patients: eight with insufficient data for analysis and three with early deaths.

Response and toxicity are shown in table 2. One partial response occurred in a patient with an indolent liposarcoma whose lesion decreased by 75% for 6 months. He had had a doxorubicin combination as a surgical adjuvant 6 years previously. The sought-for leukopenia was induced in 39 patients, seven of whom required dose escalation. Seventeen patients required dose reductions, and seven had dose escalations without leukopenia prior to disease progression. One platelet count nadir was 25,000/mm^3. There were no deaths from hematologic toxicity.

Five patients developed clinical congestive heart failure and one developed an asymptomatic decrease in ejection fraction (tables 2 and 3); all had high performance status, and none had had radiotherapy to the heart or had known risk factors for heart disease. All six patients had indolent sarcomas, receiving from three to 11 courses (median, seven) of mitoxantrone prior to documented disease progression. An additional

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[3]University of Michigan Medical Center, Ann Arbor.

[4]University of Texas at San Antonio.

[5]Ohio State University Hospital, Columbus.

[6]University of Kansas Medical Center, Kansas City.

[7]University of Arkansas for Medical Sciences, Little Rock.

Reprint requests to: Southwest Oncology Group (SWOG 8004), Operations Office, 4450 Medical Dr, San Antonio, TX 78229.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total evaluable	70
Age (yrs)	
Median: 59	
Range: 18–81	
Performance status*	
Median: 1	
Range: 0–3	
Sex	
Male	41
Female	29
Prior therapy	
Doxorubicin, alone or in combination	68
Other chemotherapy (median No. of agents, 1; range, 1–3)	25
Radiotherapy	35
Histologic subtypes	
Soft tissue sarcomas	61
Leiomyosarcoma	25
Uterine	7
Gastrointestinal	9
Other primary site	9
Liposarcoma	6
Mixed mesodermal	6
Fibrosarcoma	4
Rhabdomyosarcoma	3
Synovial cell sarcoma	3
Hemangiosarcoma	3
Neurofibrosarcoma	3
Others	8
Boney sarcomas	9
Osteosarcoma	5
Ewing's	3
Chondrosarcoma	1
No. of cycles of mitoxantrone therapy	
Median: 2	
Range: 1–16	

*SWOG criteria: 0 = Karnofsky 90%–100%; 1 = Karnofsky 70%–80%; 2 = Karnofsky 50%–60%; 3 = Karnofsky 30%–40%.

TABLE 2.—Toxicity and response

	No. of patients
Toxicity	
Leukopenia (cells/mm^3)	
None	14
2000–3999	39
1000–1999	14
< 1000	3
Gastrointestinal	
None	52
Mild/moderate nausea and vomiting	17
Mild diarrhea	1
Cardiac	6
Response to mitoxantrone	
Partial	1
Stable	15
Progression	54

14 patients received > 40 mg/m^2 of mitoxantrone (range, 45–227 mg/m^2; median, 54 mg/m^2) without developing evidence of congestive failure; all had had prior doxorubicin but in a cumulative dose range of 48–760 mg/m^2 (median, 261 mg/m^2).

DISCUSSION

In this dose schedule, mitoxantrone either lacks important activity or is cross-resistant with doxorubicin in patients with advanced sarcoma in contrast to patients with breast cancer.

Since five patients developed clinical congestive heart failure, the previously reported probable additive cardiotoxicity of mitoxantrone and doxorubicin is again suggested (1,2). The median cumulative dose of doxorubicin given to these five patients was substantially greater than that given to patients receiving similar amounts of mitoxantrone who did not develop congestive heart failure. The dose range of mitoxantrone causing de novo cardiotoxicity has not been defined in this study.

TABLE 3.—Characteristics of patients developing cardiotoxicity

Patient No.	Age (yrs)	Doxorubicin total dose (mg/m^2)	Interval between doxorubicin and mitoxantrone (mos)	Mitoxantrone total dose (mg/m^2)	Interval between last mitoxantrone dose and cardiotoxicity (wks)	Severity
1	57	430	8	72	3	Death due primarily to congestive heart failure in 3 mos
2	48	780	14	132	5	Death due primarily to congestive heart failure in 7 mos
3	73	490	1	60	6	Controlled with medication*
4	45	500	22	40	6	Controlled with medication*
5	62	220	3	119	4	Controlled with medication*
6	26	450	8	105	2	Decrease in ejection fraction only

*Digitalis and diuretics.

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Probable Cure of Small Cell Carcinoma of the Lung by Etoposide

Single-agent chemotherapy of small cell carcinoma of the lung results in an overall response rate of 30%–45% for the more active agents and a low complete response rate of < 10% (1). There have been, to the author's knowledge, no reports of long-term disease-free survival following single-agent chemotherapy.

CASE REPORT

A 59-year-old white male was noted to have a mass in his left hilum on routine chest x-ray. The mass was not visible on a chest x-ray that had been done 12 months previously. The patient was employed as an insurance agent and had smoked 30 cigarettes/day since the age of 20 years. He had a past medical history of two myocardial infarctions. He was asymptomatic and had no generalized symptoms such as loss of appetite or loss of weight.

The tumor was not visualized at bronchoscopy, and a mediastinoscopy was undertaken. Paratracheal nodes were resected, and the histology revealed infiltration by sheets of small round and spindle-shaped cells with a rather monotonous appearance and a high mitotic rate. The tumor was diagnosed initially and following review as metastatic small cell carcinoma of the lung. The patient was referred for further investigations and treatment to the Provincial Hospital, Port Elizabeth, in April 1976.

Staging investigations included liver function tests, a bone scan, and a brain scan, all of which were negative for metastases.

The patient began therapy with etoposide, given iv at a dose of 100 mg (60 mg/m^2) daily for 5 days. The course was repeated every 4 weeks and was well-tolerated without myelosuppression. There was radiological complete response after 1 month of therapy, and chemotherapy was discontinued in September 1977, after 16 courses.

The patient remained clinically and radiobiologically free of disease during subsequent follow-up. He was last seen in December 1983, 7 years and 8 months after presentation, and has been off all therapy for 6 years and 3 months.

DISCUSSION

More than 50% of patients with limited stage small cell carcinoma of the lung will achieve a complete response to current therapy regimens (2). Approximately 20% of these patients will be disease-free at 2 years, and a portion of these will remain disease-free with protracted follow-up (2,3).

It has been advocated, on the basis of tumor growth studies, that patients be disease-free for at least 4–5 years before the likelihood of cure be entertained (4).

Etoposide is among the most active, if not the most active, single agent for the therapy of small cell lung cancer (1,5). It is associated with an overall response rate of 45% and a complete response rate of 9% (1). Based on the case above, it is potentially curative.

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Raymond P. Abratt*
Wilfred Levin[1]

Department of Radiotherapy
Provincial Hospital, Port Elizabeth
and University of Cape Town
South Africa

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* *Reprint requests to:* R. P. Abratt, Department of Radiotherapy, Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa.

Pancreatitis Following Cisplatin: A Case Report[1]

Cisplatin is a highly effective agent in the treatment of selected adult and pediatric malignancies. However, its gastrointestinal side effects, the most common being nausea, vomiting, anorexia, and diarrhea (1,2), can be quite severe. Elevations of serum transaminases and asymptomatic hyperamylasemia occur rarely (2). We report a case of acute pancreatitis following cisplatin administration.

CASE REPORT

A 9-year-old white boy received cisplatin, 90 mg/m^2, and adriamycin, 75 mg/m^2, on a monthly basis for pulmonary metastases of osteosarcoma. Two cycles of chemotherapy were associated with nausea, vomiting, neutropenia, and infection and resulted in stable pulmonary metastatic disease. After receiving the third dose of cisplatin with mannitol-induced diuresis, the patient developed nausea, vomiting, and cramping abdominal pain. Hydroxyzine and morphine sulfate administration resulted in partial relief of these symptoms. Eighteen hours following the cisplatin infusion, fever (38.3°C), diffuse abdominal discomfort, and rebound tenderness occurred. Bowel sounds were hypoactive. Abdominal radiographs indicated a jejunal ileus and no free peritoneal air. The wbc count increased from an admission level of 8600/mm^3 to 17,000/mm^3. Serum amylase was 800 IU/L (normal, 20–110 IU/L). Computed tomography and ultrasound examinations failed to show dilatation of the common bile duct, and the pancreas appeared normal in size. Small bilateral pleural effusions were noted incidentally. Clindamycin and chloramphenicol were begun empirically after appropriate cultures because of the clinical setting of fever, acute abdomen, and elevated wbc counts. These drugs were discontinued after 72 hours, when all cultures failed to reveal evidence of bacterial infection. Otherwise, the patient was treated conservatively with nasogastric suction and iv fluids. Doxorubicin was given as scheduled 48 hours after the cisplatin. The patient slowly improved, with gradually decreasing abdominal tenderness. By 6 days after the cisplatin infusion, serum amylase returned to within normal limits and the patient began having bowel movements. Three weeks following the third course of cisplatin-doxorubicin, the patient underwent a right thoracotomy and resection of two pulmonary metastatic lesions. He was not rechallenged with cisplatin because this agent had failed to have significant activity against his metastases.

DISCUSSION

Vermorken and Pinedo (2) have recently reviewed the gastrointestinal toxicity of cisplatin. Ten cycles in four patients were accompanied by increases in serum amylase (2). Only mild increases were observed which generally did not exceed twice the upper limits of normal but did reach up to eight times the pretreatment levels. The pattern of serum amylase elevations was similar to the observed transaminase elevations, with a very early rise after cisplatin administration and reaching maximal levels during the first 3 days. Values returned to normal by Days 7–9. None of the individuals had symptomatic hyperamylasemia. A single case of clinical pancreatitis following intra-arterial administration of cisplatin for hepatocellular carcinoma has been noted (3).

Few antineoplastic agents have been associated with clinical pancreatitis (4). Corticosteroids and L-asparaginase are implicated as causes of pancreatitis and may be synergistic. Azathioprine, frequently used as an immunosuppressive agent in nonneoplastic conditions, is a probable etiologic agent; however, 6-mercaptopurine (the active metabolite of azathioprine) has been implicated as a cause of pancreatitis only in one case. Drugs other than antineoplastic agents suggested to cause pancreatitis included thiazides, sulfonamides, furosemide, estrogens, tetracycline, and less convincingly chlorthalidone, ethacrynic acid, phenformin, and procainamide (5). Our patient had not been exposed to any of the above agents. Other factors known to cause pancreatitis, including alcohol ingestion, biliary tract diease, recent surgery, trauma, mumps, and viral hepatitis, were not identified in our patient.

The pathophysiology of the association of pancreatitis and cisplatin is unclear. Two possible mechanisms could be considered. First, cisplatin may have caused direct injury to pancreatic cells causing release of amylase. Second, vomiting may have caused severe irritation of the duodenal mucosa and the sphincter of Oddi. Morphine may have then aggravated spasm of the sphincter causing the clinical presentation. The significance of this report is to highlight a possible toxic effect of cisplatin and to stress the importance of monitoring amylase levels during early trials of platinum analogs.

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Nancy Bunin
William H. Meyer*
Division of Hematology-Oncology

Michael Christensen
Division of Pharmacokinetics and Pharmacodynamics

Charles B. Pratt
Division of Hematology-Oncology

St. Jude Children's Research Hospital
332 N Lauderdale
Memphis, TN 38101

July 10, 1984

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* To whom reprint requests should be sent.

Endometrial Adenocarcinoma in Breast Cancer Patients Receiving Antiestrogens

Tamoxifen, structurally similar to diethylstilbestrol and classified as an antiestrogenic agent, has been employed in the management of breast cancer and, more recently, metastatic endometrial carcinoma (1,2). Generally considered to be a safe drug with minimal side effects, tamoxifen has had expanding clinical application including adjuvant therapy of breast cancer.

Scattered reports in the literature have described estrogenic effects in women receiving tamoxifen (3–5). These and our own observations of endometrial cancer developing in patients treated with tamoxifen for breast cancer have stimulated this report.

CASE REPORTS

Patient 1

This 50-year-old premenopausal patient was admitted for evaluation of abnormal uterine bleeding and a Pap smear showing cells suspicious for adenocarcinoma. Fourteen months prior to this, a left modified radical mastectomy had been performed for infiltrating duct carcinoma with metastases to one lymph node. Estrogen and progesterone receptor proteins were positive. The patient subsequently received a year of cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone (CMFVP) and tamoxifen, 10 mg twice daily, which was finished 6 weeks prior to the present admission. A stage I FIGO grade 1 endometrial adenocarcinoma was treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy, which showed tumor infiltrating into the inner one-third of the myometrium. The endometrial tissue had estrogen receptor levels of 29.2 fmols/mg and progesterone receptors of 117.6 fmols/mg of protein. There was no evidence of metastatic breast cancer.

Patient 2

This 56-year-old patient presented with postmenopausal vaginal bleeding. Nine years prior to admission the patient had used conjugated estrogens for 4 years. Her last menstrual period had been 7 years previously and she had stopped estrogen therapy 5 years prior to this admission. Eighteen months prior to this admission she had a right radical mastectomy for infiltrating duct carcinoma with two of 20 nodes positive. Estrogen receptors were positive; progesterone receptors, negative. She was receiving her seventh month of CMFVP and tamoxifen, 10 mg twice daily, when the endometrial cancer was diagnosed. A total abdominal hysterectomy and bilateral salpingo-oophorectomy showed a grade 2 adenocarcinoma involving the inner one-third of the myometrium. There was no evidence of metastatic breast cancer. She subsequently received 4400 rads of pelvic irradiation and shows no evidence of either malignancy 2 years later.

Patient 3

This 72-year-old woman was admitted for postmenopausal bleeding. She had had a right mastectomy 13 years previously and a left mastectomy 2 years prior to this admission for bilateral breast cancers; receptor status was not known. Liver metastases were diagnosed and because of her age, her postmenopausal status, and the desultory nature of her disease, she was treated with tamoxifen, 10 mg twice daily, for 14 months. At that time a stage I FIGO grade 1 endometrial carcinoma, estrogen receptor-positive, was treated by a total hysterectomy and bilateral salpingo-oophorectomy. Postoperatively she continued tamoxifen treatment and died 19 months later with metastatic breast cancer.

DISCUSSION

Endometrial cancer, an estrogen-dependent tumor, was diagnosed in one premenopausal and two postmenopausal women with breast cancer who had been receiving the antiestrogen tamoxifen, 20 mg daily, for 12, 7, and 14 months. An increased incidence of endometrial cancer

in all patients with breast carcinoma has been described, leading to speculation about the role of the endogenous estrogen milieu as a possible common etiology. Over the 2-year period during which the endometrial cancer cases were diagnosed in the two patients receiving adjuvant chemotherapy, 200 patients received adjuvant chemotherapy for breast cancer at our institution. Approximately one-half of the women received tamoxifen. With an incidence of endometrial cancer in the United States of approximately 25 cases per 100,000 women, the expected incidence in our patients would be 0.05 cases. With two cases diagnosed in the adjuvant group taking tamoxifen over this period, there appears to be an increase in the observed:expected incidence.

The effect of tamoxifen on an intact hypothalamic-pituitary-ovarian axis and cycling endometrium is complex, as indicated when endocrine status and endometrial changes were evaluated in healthy premenopausal women who were given 20 mg of tamoxifen daily (3,4). Tamoxifen may act directly on the ovary to transiently elevate serum estrogens to several times normal without intermediary gonadotropin elevation, or it may cause decreased prolactin which augments ovarian stimulation in the presence of normal levels of gonadotropins (3). Endometrial biopsies obtained in various phases of the menstrual cycle showed no effect on the proliferative phase but did show retarded development of secretory endometrium on Days 7-8 of the luteal phase, consistent with maturation of multiple ovarian follicles and an antiprogesterone effect on the endometrium by tamoxifen (4). Although there is no elevation in serum estrogen in postmenopausal women receiving tamoxifen, an estrogenic effect on the vaginal epithelium in this group of patients has been described (5). There is little information about the agent's action on the postmenopausal endometrium.

The clinical efficacy of tamoxifen used in advanced breast cancer has been established and an expanded role in adjuvant therapy is under evaluation. In premenopausal women with intact ovarian function, the increased serum estrogen levels and the estrogenic and antiprogesterone effects on the genital organs attributed to this drug may be significant. The role of tamoxifen in the development of these cases of endometrial carcinoma is not clear. There is need for more information about tamoxifen's action at the level of the endometrium in breast cancer patients. A study is planned to evaluate the endometrial response in both pre- and post-menopausal breast cancer patients receiving adjuvant chemotherapy consisting of CMFVP with tamoxifen. Gonadotropins, estrogen, progesterone, prolactin, and the karyopyknotic index of vaginal epithelium will be measured and correlated with endometrial biopsies.

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Maureen A. Killackey
Gynecology Service
Department of Surgery

Thomas B. Hakes*
Solid Tumor Service
Department of Medicine

Virginia K. Pierce[1]
Gynecology Service
Department of Surgery

Memorial Sloan-Kettering Cancer Center
1275 York Ave
New York, NY 10021

July 20, 1984

[1]We thank James Woodruff, MD, for reviewing the pathologic material from the cases presented.

* To whom reprint requests should be sent.

Etoposide in the Treatment of Multifocal Eosinophilic Granuloma

Although not considered as a neoplastic disease on a histopathological basis, the multifocal eosinophilic granuloma may pursue a progressive and fatal course (1). Patients with multifocal eosinophilic granuloma with one or more organ system involved are usually treated by radiotherapy, corticosteroids, and/or chemotherapy with significant morbidity and toxicity (1). Etoposide, an epipodophyllotoxin, is a drug of low toxicity and proved efficacy in the treatment of neoplasms of histiomonocytic lineage (2,3); however, to the best of our knowledge, no cases of multifocal eosinophilic granuloma treated with etoposide have been communicated so far. We report

here the use of this drug in the treatment of a patient with multifocal eosinophilic granuloma.

CASE REPORT

A 48-year-old white woman was referred to our center in May 1980, because of a loosening of her teeth, ulcerative vulvar lesions, severe pain in the humeral region, and bilateral hemianopsia of 6 months' duration. She had had a diagnosis of diabetes insipidus 5 years before. No history of dyspnea, coughing, otitis, or mastoiditis was referred to. Shortly before admission, the patient's diuresis had been 9–11 L of urine/day. Neither palpable lymph nodes, hepatomegaly, splenomegaly, skin lesions, nor exophtalmus was present. Chest x-rays as well as pulmonary function tests were normal.

Hemoglobin was 13.5 g/dl; wbc count, 9.1 × 10^9/L with 8% eosinophils; and the platelet count, 340 × 10^9/L. Erythrocyte sedimentation rate was 20 mm during the first hour. Plasma osmolarity was 327 mOsm/L, and serum sodium concentration was 147 mEq/L. Urine specific gravity was 1003, urine osmolarity 96 mOsm/L, and urine sodium concentration 15 mEq/L. Renal and hepatic function tests, glucose, calcium, phosphorus, and lipids were normal. Bone marrow aspirate was normal. Radiological bone studies revealed osteolytic lesions in the right humerus and mandible. Histological and ultrastructural studies of the bone, vulvar, and gingival lesions were diagnostic of multifocal eosinophilic granuloma (4). Treatment with etoposide, 200 mg/day orally for 5 days every 3 weeks, was started. After the first cycle, bone pain disappeared and diuresis decreased from 11.1 to 2.5 L/day. Bilateral hemianopsia and ulcerative vulvar lesions gradually improved after administration of the second cycle. Three additional cycles of etoposide were given and treatment was discontinued. Overall, the hematological, hepatic, and clinical tolerance to treatment was fairly good.

Five months after the last cycle of etoposide, ulcerative gingival and vulvar lesions, polydipsia, polyuria (9–10 L/day), and right pelvic pain were apparent. An osteolytic lesion in the right ischium was detected. Treatment with etoposide (200 mg/day orally × 5) was reinitiated with 4-week intervals between each cycle. The vulvar lesions and right ischium osteolytic lesion gradually disappeared and, after 15 months of treatment, the patient was completely asymptomatic. Daily diuresis was 2–4 L. Plasma osmolarity was 300 mOsm/L; serum sodium concentration, 145 mEq/L; urine specific gravity, 1007; urine osmolarity, 240 mOsm/L; and urine sodium concentration, 50 mEq/L.

DISCUSSION

The treatment of multifocal eosinophilic granuloma depends on the age of the patient and the extent of the lesion (1). Patients > 2 years of age and with one or more organ system involved [stage II according to Greenberger et al (1)] should be treated with radiotherapy, corticosteroids, and/or chemotherapy (1). This disorder has been reported to respond to vinblastine, methotrexate, chlorambucil, or cyclophosphamide, although with significant morbidity and toxicity in some cases (1,5). In our case, because of the important systemic involvement, the low toxicity of etoposide and its proved efficacy in the treatment of neoplasms of histiomonocytic lineage (2–3), we decided to administer etoposide. The benefits of this treatment were apparent from the first cycle of treatment, although the reappearance of the lesions when the treatment was discontinued made it necessary to reinitiate etoposide. Presently, 3½ years after diagnosis, the patient remains asymptomatic and under treatment (200 mg/day orally × 4 every 30 days) with excellent tolerance.

Etoposide could be a useful drug in the treatment of multifocal eosinophilic granuloma, with great efficacy, low toxicity, and no need for additional radiotherapy or corticosteroids.

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Alvaro Urbano-Márquez
Ramón Estruch
José M. Fernandez-Huerta

Department of Internal Medicine

Emilio Montserrat
Ciril Rozman

Postgraduate School of Hematology "Farreras Valentí"

Hospital Clínico y Provincial
University of Barcelona
Casanova, 143
Barcelona-36, Spain

July 23, 1984

Clinical Evidence of a Cumulative Effect of High-Dose Cytarabine on the Cerebellum in Patients With Acute Leukemia: A Leukemia Intergroup Report[1]

Several investigators have reported the association of signs and symptoms of cerebellar toxicity with the use of high-dose cytarabine (HD-ara-C) (2–3 g/m^2 twice daily by bolus infusion for 3–6 days) for the treatment of patients with refractory lymphoma and acute leukemia (1–5). Although the mechanism is not known, postmortem examination has shown degeneration of Purkinje cells, primarily in the lateral hemispheres (4,5).

We have recently seen six patients who did not have neurologic complications with their first course of HD-ara-C but did develop cerebellar toxicity with subsequent exposure to lower total doses of ara-C, including one patient (No. 1), who had recurrence of cerebellar symptoms when subsequently treated with a course of standard-dose ara-C (100 mg/m^2/day as a continuous infusion over 10 days). The relevant clinical details of these patients are presented in table 1. As shown, cerebellar toxicity was associated with a course of treatment in which the total dose of ara-C administered was lower than what had been given in previous uneventful courses. In all cases the HD-ara-C was administered as an infusion in 250 ml of 5% dextrose in water over 60–90 minutes. None of the patients had a prior history of neurologic problems or of excess alcohol intake and none had received prior central nervous system therapy. Although four of the six patients received other drugs with known neurologic side effects, none of these drugs are usually associated with primary cerebellar dysfunction. Moreover, the neurotoxicity associated with these drugs usually resolves quickly as the drug is withdrawn, while in our patients, symptoms and signs persisted from 4 days in Patient 1 to as long as 7 months in Patient 2. An interaction of HD-ara-C with other drugs cannot be ruled out as a contributing factor to cerebellar toxicity.

Cerebellar toxicity has not previously been reported with conventional doses of ara-C. Intrathecal ara-C has been associated with a variety of neurologic complications including headache, meningismus, myelinopathy, and in a few cases progressive necrotizing encephalopathy; but, to date, it has not been associated with cerebellar toxicity.

Lazarus et al (3) noted an increasing incidence of neurologic symptoms with increasing total doses of ara-C on initial exposure to the drug in high doses. Central nervous system toxicity was seen only in patients who received total doses > 36 g/m^2, which is consistent with our experience (table 1). In our patients the total dose of ara-C received, including all courses of ara-C, ranged from 48 g/m^2 in Patient 2 to 90 g/m^2 in Patient 3.

The uniqueness of our observation in these patients is the development of clinical cerebellar toxicity with a course of treatment that was associated with a smaller ara-C dose than had previously been administered without toxicity. Lazarus et al (3) reported cerebellar toxicity with the initial dose of HD-ara-C given. This pattern of toxicity suggests that use of HD-ara-C may be associated with subclinical cerebellar damage that becomes manifest clinically with subsequent therapy. This may represent a cumulative effect of the drug on the cerebellum. Comparative pathological studies of affected patients and patients who have received the drug without clinical sequelae are necessary to determine the precise mechanism of this effect.

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TABLE 1.—Patient characteristics

Patient No.	Age (yrs)	Sex	Diagnosis*	Previous ara-C† total dose (g/m^2)	HD-ara-C total dose/course (g/m^2) — 1	2	3	4	Other drugs in use at time of development of cerebellar toxicity‡
1	69	F	Secondary ANLL	0	36	15§	0	0	Allopurinol, metoclopramide
2	41	F	Secondary ANLL	0	36	12§	0	0	Cotrimoxazole
3	63	M	Secondary ANLL	0	36	12	18	24§	Cimetidine, THC
4	57	M	Relapsed ANLL	8.2	36	12§	0	0	Metoclopramide
5	61	F	Relapsed ANLL	5.9	36	18§	0	0	Chlorpromazine, THC
6	43	F	Relapsed ANLL	6.0	36	30§	0	0	

*ANLL = acute nonlymphocytic leukemia.

†Patients 4, 5, and 6 had previously received standard-dose ara-C (*see* text) as part of initial induction therapy and consolidation.

‡THC = Δ-9-tetrahydrocannabinol.

§Course of HD-ara-C associated with cerebellar toxicity; in Patient 1 a second episode of cerebellar toxicity occurred on exposure to standard-dose ara-C (*see* text).

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Ann Benger
George P. Browman*
Irwin R. Walker

Ontario Cancer Foundation, Hamilton Regional Center
Hamilton Civic Hospitals and Chedoke-McMaster Hospital
Hamilton, Ontario, Canada

Harvey D. Preisler

Roswell Park Memorial Institute
Buffalo, NY

Jack Goldberg

Upstate Medical Center
Syracuse, NY

July 24, 1984

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* *Reprint requests to:* Dr. G. P. Browman, Ontario Cancer Foundation, Hamilton Regional Center, 711 Concession St, Hamilton, Ontario L8V 1C3, Canada.

Dynamic Left Ventricular Outflow Obstruction and Myocardial Infarction Following Doxorubicin Administration in a Woman Affected by Unsuspected Hypertrophic Cardiomyopathy

Pharmacological and experimental studies have shown the possibility that doxorubicin increases the levels of catecholamines[1] and that propranolol may decrease the incidence of acute arrhythmias (1). These data support the hypothesis that the circulating catecholamines, which have been acutely increased by the drug, could contribute to heart damage due to doxorubicin.

We report a case of a patient who had been surgically treated for anaplastic cancer of the thyroid. A few hours after the third monthly dose of doxorubicin, this patient had clinical-echocardiographic evidence of temporary dynamic obstruction of the outflow tract of the left ventricle and presented a clinical picture of myocardial infarction which might have been due to catecholaminic stimulation of the drug.

CASE REPORT

A 58-year-old woman who had recently been surgically treated for anaplastic cancer of the thyroid was admitted to our hospital for treatment with doxorubicin. Before and during this treatment she had been receiving sodium thyroxine (300 μg daily) for 1 month. At that time, the findings on physical examination were unremarkable. There was no heart murmur. The heart was normal on x-ray and the electrocardiogram showed aspecific alterations of the T wave. On August 15, and September 15, our patient received the first two doses of doxorubicin (45 mg/m^2), with no side effects. On October 15, she received a third dose of the drug. Two hours after administration the patient complained of severe malaise and chest pain which continued for 4 hours. Findings on physical examination were: tachycardia (130/minute) and a 4/6L diamond-shaped murmur on apex and centrum cordis. Blood pressure was 160/90 mm Hg. The electrocardiograms showed a picture of progressive anterior and inferior subepicardial ischemia which still stands (fig 1). There was a moderate increase of creatine phosphokinase and myocardial blood-creatine phosphokinase. The echocardiogram recorded findings of obstructive hypertrophic subaortic stenosis with septal thickening, a systolic anterior motion of the mitral valve, and a midsystolic closure of the aortic valve cusps (figs 2 and 3). The patient was treated with propranolol, and the sodium thyroxine dose was decreased. The following day there was no systolic murmur, and the echocardiogram showed no systolic anterior motion of the mitral valve and no midsystolic closure of the aortic valve cusps.

DISCUSSION

Pharmacological and experimental studies have shown the possibility that doxorubicin increases the levels of circulating catecholamines,[1] so that propanolol could decrease the incidence of acute arrhythmias (1).

Our patient, a few hours after the third administration of doxorubicin, complained of severe malaise and chest pain. Physical examination showed a 4/6L diamond-shaped heart murmur which had not been recognized previously. The echocardiogram showed findings of hypertrophic subaortic stenosis which previously had been unsuspected, with evidence of systolic anterior movement of the mitral valve and midsystolic closure of the aortic valve cusps. The following day the physical signs and echocardiographic data related to dynamic ventricular outflow obstruction were no longer appreciable.

These data could suggest that in our patient doxorubicin might have had a strong effect of adrenergic stimulation provoking dynamic left ventricular outflow

[1]Bristow M, and Daniels J. Methods for monitoring anthracycline-induced cardiomyopathy. Presented at a National Cancer Institute Symposium, Sept 1977.

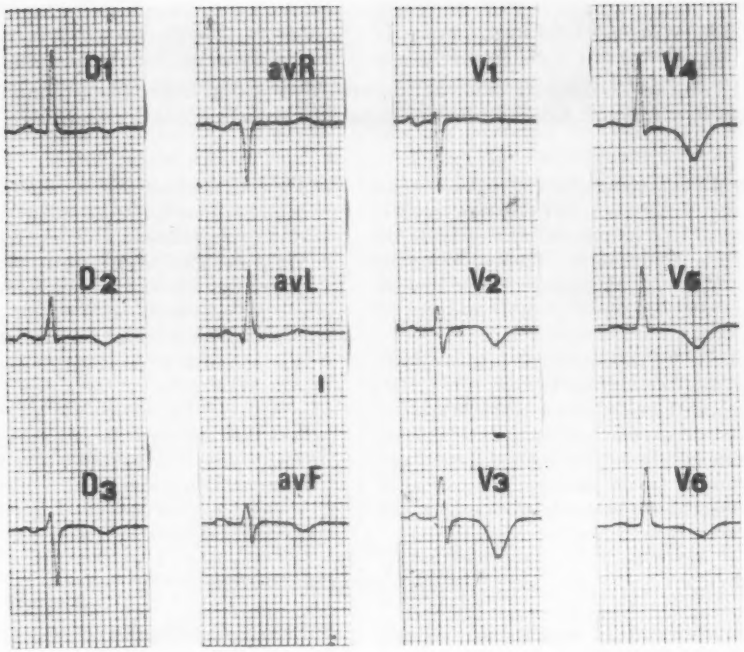

FIGURE 1.—ECG after the third dose of doxorubicin showing a picture of anterior and inferior subepicardial ischemia.

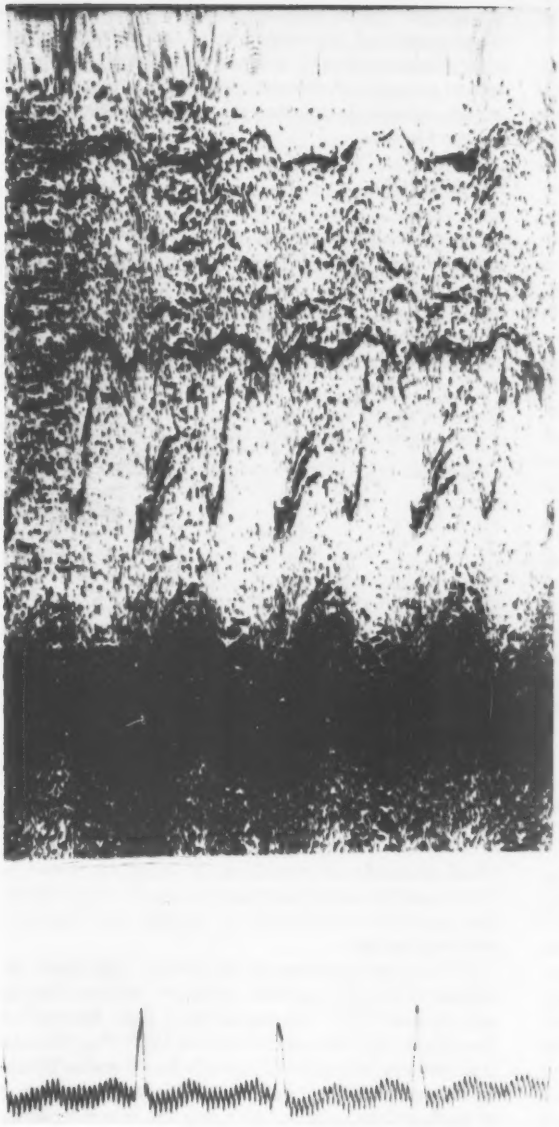

FIGURE 2.—M-mode echocardiography showing septal thickening and systolic anterior motion of the mitral valve.

FIGURE 3.—M-mode echocardiography showing a mid-systolic closure of the aortic valve cusps.

obstruction, similar to that caused by pharmacological provocation (isoproterenol).

Although effects of adrenergic stimulation such as those provoked in animals have only been suspected in humans, it is not improbable that they may be the cause of some reported cases of heart arrest following anthracyclinic administration (2). In some of these cases ventricular arrhythmias have been observed (2). In our case it is possible to formulate the hypothesis that the adrenergic effect of doxorubicin could have been increased by the high doses of thyroxine administered, as it is known that thyroid hormones make the receptors more responsive to the effects of the catecholamines. Moreover, it is necessary to emphasize that doxorubicin has been reported to decrease the mitochondrial content of Q_{10} coenzyme (3), which has an important role in oxidative phosphorylation. The thyroid hormones also dissociate oxidative phosphorylation, and an analogue structure of such hormones with that of quinones has been noted (3). It is possible that the combined action of the two drugs (doxorubicin and thyroxine) that act as oxygen wasters could partially explain the acute coronary event in this patient. However, it is possible that the acute coronary event may have been caused by dynamic obstruction of the left ventricle. On the contrary, we cannot exclude the possibility that a "chance" ischemic event could have caused the clinical-echocardiographic aspects of dynamic ventricular outflow obstruction, but the fact that the ischemic event took place shortly after administration of the drug does not support this hypothesis. Moreover, there have been other reports of myocardial infarction occurring soon after administration of anthracyclinic drugs (4). The nature of our patient's disease dissuaded us from performing an angiography to prove the presence of concomitant coronary lesions.

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Luigi Mancuso
Salvatore Marchi
Augusto Canonico

Divisione di Cardiologia
Ospedale V. Cervello
Via Trabucco 180
Palermo, Italy

July 30, 1984

Possible Interactions Between Warfarin and Antineoplastic Drugs

A recent letter describes a probable interaction between warfarin and etoposide or vindesine (1). In 1982, Booth and Weiss (2) reported a similar prolongation of the prothrombin time (PT) in a patient with breast carcinoma on a stable dose of warfarin. The patient presented with an iliopsoas hematoma 3 weeks after resumption of adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). We present an additional three cases of possible interactions between warfarin and antineoplastic drugs and suggest that this drug toxicity is more common than previously reported.

A 70-year-old postmenopausal woman with breast carcinoma (T2N1M0) had a modified radical mastectomy followed by adjuvant cyclophosphamide, methotrexate, and 5-FU (CMF). The patient had a right femoral vein thrombosis after the second cycle of CMF, requiring heparin and warfarin anticoagulation. The PT ranged from 18.2 to 21.0 seconds on a stable dose of warfarin. By Day 15 of each subsequent cycle, the PT increased to 44.2, 39.0, 31.0, and 29.0 seconds, respectively, lasting 48-72 hours. These episodes were complicated by epistaxis on each occasion and by gross hematuria during the first episode; the complications responded to cessation and lowering of warfarin dosage.

A 57-year-old postmenopausal woman with breast carcinoma (T1N1M0) received primary radiation therapy and adjuvant CMF. The patient had a right femoral vein thrombosis after the second cycle of CMF. The PT stabilized between 14.8 and 17.2 seconds over 3 weeks. On Day 15 of each subsequent cycle, the PT increased to a range of 24.6-26.0 seconds for 48 hours and was complicated by epistaxis on one occasion and by microscopic hematuria during subsequent episodes.

A 62-year-old man with diffuse mixed lymphoma received combination chemotherapy including cyclophosphamide, doxorubicin, etoposide, mechlorethamine, vincristine, procarbazine, methotrexate, and prednisone (ProMACE-MOPP). After the sixth cycle, the patient developed a pulmonary embolus and required systemic anticoagulation. The PT was maintained between 18.0 and 20.0 seconds on a stable warfarin dose. In the midst of

three subsequent cycles, after Days 1 and 8 of chemotherapy, the PT rose to 45.0, 30.0, and 36.0 seconds, respectively. The patient noted a subconjunctival hemorrhage during the first episode of PT prolongation. After cessation of warfarin, the PT returned to normal within 1 week.

These three cases suggest a possible interaction between warfarin and chemotherapeutic agents. The antineoplastic drugs may impair vitamin K absorption or may interfere with warfarin during absorption, vascular transport, degradation, or excretion. Prior trials employing warfarin as a cytotoxic adjunct to chemotherapy did not report difficulty in stabilizing the PT (3,4). Trials in progress, such as the phase III study of warfarin in small cell carcinoma (5), may help to define the frequency and mechanism of this interaction.

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Eric J. Seifter
Burke J. Brooks, Jr
Walter J. Urba

Clinical Oncology Program
NCI-Navy Medical Oncology and Medicine Branches
Bldg 1, Rm 415, Naval Hospital
Bethesda, MD 20814

August 10, 1984

New Cancer Treatments: Infusional Chemotherapy and Bone Marrow Transplantation

Boston, Massachusetts, March 7-8, 1985

This annual cancer symposium of the New England Deaconess Hospital will be divided into two sessions. A session on infusional chemotherapy addresses hepatic artery infusion, including technical aspects, with the goal of establishing the present status of hepatic arterial infusion in cancer management. The second session will bring together leaders in the field of bone marrow transplantation to describe the techniques and applications of allogeneic and autologous bone marrow transplantation for hematologic malignancies and their emerging application for treatment of resistant solid tumors such as colon cancer, melanoma, and lung cancer. The course directors are Drs. Murray M. Bern and Jacob J. Lokich of the New England Deaconess Hospital.

For further information, contact: Gwen Schuster, Department of Continuing Education, Harvard Medical School, Boston, MA (telephone: 617-732-1525).

Prostatic Carcinoma: New Frontiers

Stanford, California, March 21-23, 1985

The Division of Urology, Stanford University School of Medicine, is sponsoring this multidisciplinary course. It will present an integrated overview of the frontiers of knowledge about prostate cancer to the urologist, oncologist, pathologist, and research scientist.

For further information, contact: Office of Postgraduate Medical Education, Rm TC-129 Medical Center, Stanford, CA 94305 (telephone: 415-497-5594).

Fourth Annual Symposium on Breast Neoplasia

Vail, Colorado, March 23-30, 1985

This is a continuing education program offering 23 contact hours of credit. Tuition is $390 for physicians and $330 for residents.

For further information, contact: Symposia Medicus, 2880 Shadelands Dr, Suite 404, Walnut Creek, CA 94598 (telephone: 415-935-7889).

Ureteropyeloscopy Seminar

New York, New York, April 12-13, 1985

The Memorial Sloan-Kettering Cancer Center is offering this postgraduate course devoted to the new technique of transurethral ureteropyeloscopy. Mornings will be devoted to didactic sessions; "hands-on" workshops for small groups, using endoscopic equipment and animal models, are planned for the afternoons.

The course director is William R. Fair, MD, of the Center's Urology Service. The program has been approved for 12 hours of credit, Category I.

For further information, contact: CME Conference Planning Office, C-180, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (telephone: 212-794-6754).

Carcinoma of the Lung—A Twentieth Century Dilemma

Spartanburg, South Carolina, April 18–19, 1985

This Ninth Annual Spring Oncology Seminar sponsored by Spartanburg General Hospital will consist of an overview session and sessions on non-small cell and small cell lung cancer. It will be held at the Ramada Inn of Spartanburg and qualifies for 11 hours of Category I AMA credit.

For further information, contact: Colleen Miller, CME Coordinator, Spartanburg General Hospital, 101 E Wood St, Spartanburg, SC 29303 (telephone: 803-573-6280).

International Symposium on Labelled and Unlabelled Antibody in Cancer Diagnosis and Therapy

Baltimore, Maryland, September 12–13, 1985

This symposium, to be held at The Johns Hopkins Medical Institutions, will include sessions on monoclonal antibody in therapy, treatment of bone marrow with antibody for transplantation, radiolabeled antibody in diagnosis, dosimetry and physics of radiolabeled antibody, radiobiology of low-dose-rate radiation, therapeutic approaches with drug labels, radiolabeled antibody, and new diagnostic and therapeutic approaches.

The deadline for submission of abstracts is *May 1, 1985.*

For further information, contact: American College of Radiology, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3150).

Conference on Chemical Modifiers of Cancer Treatment

Clearwater, Florida, October 20–24, 1985

This conference, the fifth in a series of international conferences on radiation sensitization, radioprotectors, and chemical modifiers of cancer treatment, will be held at the Sheraton-Sand Key in Clearwater. The subject of the conference is the use of chemical agents (primarily radiosensitizers, radioprotectors, repair inhibitors, and agents which improve tumor oxygenation) to modify the response of tumor and/or normal tissues to the cytotoxic effects of radiation or chemotherapeutic drugs. Basic scientists in chemistry and biology and clinicians in radiotherapy and chemotherapy will exchange information and ideas on current research, future efforts, and design and implementation of new clinical trials.

The program will consist of eight sessions. It is hoped that financial assistance can be offered to a number of young investigators. The deadline for submission of abstracts, poster presentations, and requests for travel assistance is *June 15, 1985.*

For further information, contact: Ms. Suzanne Bohn, American College of Radiology, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3150).

SOMPS First International Congress on Neo-Adjuvant Chemotherapy

Paris, France, November 7–9, 1985

Several international experts will participate in this congress, sponsored by the Service d'Oncologie Médicale Pitié-Salpétrière (SOMPS). Abstracts should be submitted to the organizing committee by *July 1, 1985.*

For further information, contact: SOMPS—First International Congress on Neo-Adjuvant Chemotherapy, Pavillon Jacquart, Hôpital de la Salpétrière, 47, boulevard de l'Hôpital, 75651 Paris Cedex 13, France (telephone: 570-28-29 or 570-28-30).

Society for Biological Therapy: Membership Information

The purpose of the Society for Biological Therapy is to bring together people who are actively investigating biologicals and biological response modifiers in the treatment of cancer and to maintain meaningful communication with other relevant scholarly societies.

There are five categories of membership: active, emeritus, honorary, associate, and corporate. Appli-

cants are nominated to the Membership Committee by three active members. A two-thirds majority of the Membership Committee is required for submission of the membership application to the Board of Directors. Members are elected by a majority vote of the Board of Directors.

For further information, contact: John Whisnant, MD, Burroughs Wellcome Co, 3030 Cornwallis Rd, Research Triangle Park, NC 27709.

Publication of *Workshop Conference on Hyperthermia in Cancer Treatment*

The current status of hyperthermia in cancer therapy is discussed in this supplement to the October 1984 issue of the journal *Cancer Research. Workshop Conference on Hyperthermia in Cancer Treatment* (J. P. Lowenthal, editor; ISSN 008-5472; $20 plus postage and handling) may be purchased directly from the printer: Waverly Press, 428 E Preston St, Baltimore, MD 21202, Attn: Bill Catterton.

CORRECTION

In the article "Etoposide Infusions for Treatment of Metastatic Lung Cancer" by W. P. Steward, N. Thatcher, J. M. Edmundson, W. Shiu, and P. M. Wilkinson (Cancer Treat Rep 68:897–899, June 1984), the results quoted in the section on Pharmacokinetics were results for a 30-minute infusion. Data for a 24-hour infusion are as follows: peak serum concentration, 17.5 μg/ml; area under the curve, 1100 μmols.L/hour.

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